

IRI Report No. 2195

HMX: 13 Week Toxicity Study in Mice by Dietary Administration

Final Report by:

D.J. Everett S.M. Maddock

3/ July, 1985



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Abstract

Mice were fed diets containing HMX for 13 weeks. Dose levels for males were 0, 5, 12, 30, 75 or 200 mg HMX/kg/day. Female mice received 0, 10, 30, 90, 250 or 750 mg HMX/kg/day.

Mortalities attributable to HMX at 200 mg HMX/kg/day amongst males and at 250 and 750 mg HMX/kg/day amongst females. Occasional deaths at lower dose levels were of uncertain aetiology.

No marked effects on body weight were noted although food consumption was reduced amongst higher dosed males and females.

There were slight but equivocal changes in haematological and clinical chemical observations.

Neither gross autopsy nor histopathology revealed any findings likely to be associated with the administration of HMX.

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FOREWORD

"I, the undersigned, hereby declare that this work was performed under my supervision, according to the procedures herein described and that this report represents a true and accurate record of the results obtained."

A. S. W.

A.B. Wilson, B.V.Sc., M.R.C.V.S.,
D.A.B.T.
Principal Investigator



The title on the front cover is correct for this report.
Per Ms. Virginia Miller, AMR&DC

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Project No. 416877



Report No. 2195

QUALITY ASSURANCE AUTHENTICATION

The conduct of this study has been subjected to periodic inspections by the IRI Quality Assurance Unit. The dates of inspection are given below.

IRI Project No. 416877

Report No. 2195

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19 January 1981 17 February 1981 27 February 1981 13 April 1981 24 April 1981

This report has been audited by the Quality Assurance Personnel according to the appropriate Standard Crerating Procedure. The report is considered to describe accurately the methods and procedures used in the study and the original data generated during the study.

Signed:

Model Waddel (Quality Assurance

Manager)

Date: 3rd Maul 1986

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SUMMARY

The objective of this study was to obtain information on the toxic effect of Octahydro-1,3,5,7,tetranitro-1,3,5,7-tetra-zocine (HMX) when administered via the diet for 13 weeks.

Five groups of 20 male B6C3F1 mice were dosed with concentrations of HMX in diet to give dose levels of 5, 12, 30, 75 or 200 mg/kg/day for at least 95 days. Five groups of 20 female B6C3F1 mice were similarly dosed at levels of 10, 30, 90, 250 or 750 mg HMX/kg/day. In addition 20 male and 20 female mice received untreated diet and acted as controls.

All animals which died or were killed $\underline{\text{in extremis}}$ were necropsied. All surviving animals were killed and necropsied after completion of 13 weeks of treatment.

The results can be summarised as follows:-

Mortality:

		m		ales X/kg	/day			mg		male /kg/		
	0	5	12	30	75	200	0	10	30	90	250	750
No. of Deaths	0	0	0	1	2	13	1	0	1	0	12	20
% Mortality	0	0	0	5	10	65	5	0	5	0	60	100

Clinical Signs: Possible slight increase in excitability

in top dose males and females, largely masked by general excitability of B6C3F1

mice.

Body Weight: No marked effect on body weight was noted

in either sex.

Food Consumption: Reduced food consumption in male mice

receiving 75 or 200 mg HMX/kg/day and in female mice receiving 750 mg HMX/kg/day.

Water Consumption: No intergroup differences in water

consumption were noted.

Achieved Dosage: This was considered to fall within accept-

able limits.

Ophthalmoscopy: No lesions were seen which could be

attributed to dosing with HMX.

Laboratory Investigations

Haematology: No dose-related trends were noted in male

mice. A slight reduction in haemoglobin concentration and slight increases in white blood cell and lymphocyte counts were seen

in female mice receiving HMX.

Clinical Chemistry: Glucose concentration, alanine amino-

transferase and alkaline phosphatase

values were all slightly depressed in male mice receiving HMX. Female mice receiving HMX also showed a slight depression in

alkaline phosphatase levels.

Urinalysis: Male mice receiving HMX produced slightly

more acidic urine of lower specific gravity than controls. Female mice receiving HMX produced urine of slightly higher specific

gravity than controls.

Terminal Studies

Organ Weights: A slight increase in the absolute and

relative brain weights of male mice receiving HMX was noted. Female mice receiving

HMX also showed a slight increase in

absolute brain weight compared with controls. Absolute and relative spleen weights were slightly reduced in female mice receiving

HMX.

Gross and Histo-

pathology:

There were no dose related findings.

INTRODUCTION

Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine (HMX) is found in the waste-water effluent as a byproduct in production of the high explosive RDX. This 13 week dietary study in mice forms part of a series of animal toxicity, pharmacokinetic and metabolic studies intended to evaluate the toxicity of HMX.

The experiment was undertaken at the Elphinstone Research Centre of Inveresk Research International Limited, within the Modular Animal Maintenance System (MAMS) complex. It was started on 16 January 1981 and necropsies were completed on 23 April 1981.

The Sponsor for this work was US Army Medical Research and Development Command.

All data generated and recorded during this study will be stored in the Scientific Archives of Inveresk Research International Limited.

MATERIALS AND METHODS

Test Substance

A total of 14.9 kg (dry weight) of HMX was received from the Royal Ordanance Factory, Somerset, via Nobels Explosive Company, Stevenson over the period 27 June 1980 to 2 February 1981. The test compound was supplied wetted with 15.25% water and was a grey paste. Prior to use, individual 50 g lots were dried in a water jacketed oven at 85-90°C until constant dry weight was achieved. The white powder obtained from this process was sieved through a nylon mesh before use.

Methods

Design Conditions

Animals

Three hundred and twenty six B6C3F1 mice, divided equally by sex were obtained from Charles River Limited, Wilmington, Massachusetts, U.S.A. on 7 January 1981. They were ordered in the weight range 12-15 g on arrival.

One hundred and forty males and 140 females were allocated to treatment groups and were allowed 9 days acclimatisation before treatment began. One male and 2 females were replaced before treatment began and the excess animals discarded when dosing started.

Animal Receipt and Acclimatisation Procedures

The assessment of animal health status and suitability for use on study occurred in 2 stages:

(a) Shortly after arrival, 10 animals/sex were subjected to pre-experiment acceptance tests (PEAT). PEAT involved a clinical examination, necropsy, histopathological examination of major organs and evaluation of bacterial and parasitic status.

Animals were selected for PEAT firstly on the basis of clinical examination and secondly at random.

(b) Upon arrival and throughout the 9 day acclimatisation period animals were assessed for signs of disease. Animals suspected of being diseased were culled from the study and necropsy carried out. During this time 3 animals were replaced.

Housing

Mice were housed in a barrier maintained animal room at a room temperature normally of 21°C + 2°C and a relative humidity of generally between 40% and 70% (both automatically controlled), with circa 14 air changes/h. A 12 h light/dark cycle was controlled by a time switch, light hours being 0700-1900 h. Continuous monitoring of temperature and humidity was by thermohygrograph. Room location was at Elphinstone Research Centre within the MAMS complex.

Caging and Cage Sanitation

Mice were housed one animal per cage in suspended polypropylene cages (overall dimensions $480 \times 150 \times 130 \text{ mm}$) with stainless steel wire grid tops. Bedding was white wood shavings.

Cages were changed at least once each week. Each cage had a polypropylene water bottle (total capacity 300 ml) with rubber washer and melamine cap.

Diet and Water

During the course of the study tap water and a laboratory rodent diet (BP Nutrition (U.K. Limited) Expanded Ground Maintenance Diet) were available to the mice ad libitum. Typical analyses for both diet and water are presented in Appendices 1 and 2.

Animal Room Sanitation

Each morning, before other work in the room began, floors were mopped with a disinfectant solution (either 1% Tego from T.H. Goldschmidt and Company Limited or 3% Hycogen from Hy-co Products (Scotland) Limited). Each afternoon, following completion of all other work, floors were swept then washed with a disinfectant solution. Once each week, walls, ceiling, benches and racking within the animal room were washed with a disinfectant solution.

Distribution of Animals into Treatment Groups

On the day of arrival, the mice were distributed at random into the treatment groups as follows:

Upon receipt the mice were divided into 3 body weight ranges and placed into large holding cages. The cages to be used during the experiment were set up on racks and divided into sequences of 7 cages. A set of random numbers was used to assign a male of

the lowest weight range to the first cage of a designated sequence. When all animals from the lowest weight range had been allocated the highest weight range of males was used, followed by the middle weight range.

When the first cage of every sequence contained a mouse the process was continued using the second cages. This procedure was followed until 140 cages contained one male mouse. The process was then repeated using female mice and new cages.

Each mouse was ascribed a treatment group by the use of another set of computer generated random number sequences. Thus any intergroup environmental differences were minimised.

Animal Identication

Each mouse was given a unique earmark which identified it within the study and corresponded to that animal's study number.

Route and Duration of Treatment

The test compound was administered orally via the diet for a minimum of 95 consecutive days.

Dose Levels, Treatment and Groups and Animal Numbers

The dose levels ascribed to each treatment group and animal number at the start of the treatment period were as follows:

Group	Dose I	Level /kg/day)	Animal N	Numbers
	Males	Females	Males	Females
1	0	0	1-20	121-140
2	5	10	21-35	141-160
			366*	}
			37-40	ĺ
3	12	30	41-60	161-173
				374*
				175-180
4	30	90	61-80	181-200
5	75	250	81-100	201-220
6	200	750	101-120	221-240
7	0	0	241-260	261-263
,	_		1	364*
				265-280

* = Numbers 36, 174 and 264 were replaced by numbers 336, 374 and 364 respectively before treatment began.

Animals in Group 7 were intended to add to the background data available only on the clinical pathology of B6C3F1 mice as this was limited at IRI. Results obtained from these investigations are not included in this report.

Preparation of Test Diets

Fresh diets were prepared once each week. The concentration of test compound was adjusted each week to give as constant mg/kg/day dose level as possible by prediction of the mid-week body weight and weekly food consumption for the week in question. Diets were prepared by direct admixture of the requisite amount of HMX to untreated diet and blending for 20 min in a Winkworth Change Drum Tumble Mixer.

Dietary Sampling

A 100 g sample of diet from each group/sex was taken and retained immediately after diet preparation at the start of each week. These samples form part of the study archives. In addition, 3 samples each of 10 g were taken from each group/sex receiving HMX at the beginning of weeks 1, 2, 3, 4, 7, 10 and 13. These samples, together with 3 samples of 100 g control diet each sampling, were analysed at IRI.

Observations

Clinical Signs

All animals were checked early morning and later afternoon on each day for dead or moribund animals. The onset and duration of all signs of ill health or reaction to treatment were recorded after daily examination of the animals. Each animal was given a detailed physical examination for clinical signs or external lesions once a week.

Deaths

Animals dying during the study were given a detailed macroscopic examination and tissues listed under 'Post Mortem Studies' were preserved.

Body Weight

The weight of each animal was recorded at weekly intervals commencing one week before the start of treatment up until the end of treatment. In addition, body weight recording was carried out on Day 4 of each of the first 4 study weeks.

Food Consumption

The quantity of food consumed by each animal was recorded once each week commencing one week before the start of treatment and up to the end of 13 weeks dosing. The amount of food scattered by each animal was recorded.

Water Consumption

Water consumption was assessed by visual inspection of the water bottles for any intergroup differences.

Ophthalmic Examination

Ophthalmic examinations were carried out on all animals using an indirect ophthalmoscope before dosing commenced and during Week 13 of dosing.

Laboratory Investigations

Haematology

Blood was taken from the orbital sinus of mice lightly anaesthetised with ether during Week 12 of dosing. Ten mice were selected by computer generated random numbers from each group at the following mg HMX/kg/day dose levels: 03, 303, 753, 2003, 0 $^\circ$, 30 $^\circ$, 90 $^\circ$, 250 $^\circ$, 750 $^\circ$ (survivors were used where less than 10).

The following measurements were carried out on whole blood taken into E.D.T.A.:

Red cell count
White cell count
Packed cell volume
Haemoglobin concentration
Differential white cell count
Reticulocyte count
Heinz bodies

Hepato Quick tests were carried out using blood obtained by tail snip without anaesthesia.

Clinical Chemistry

Blood was collected from the vena cava at termination from the same mice bled for haematology. The following measurements were carried out on plasma taken from whole blood collected in heparin.

- 1. Asparate aminotransferase (GOT)
- 2. Alanine aminotransferase (GPT)
- 3. Alkaline phosphatase (AP)
- 4. Lactate dehydrogenase (LDH)
- 5. Blood urea nitrogen
- 6. Glucose
- 7. Albumin
- 8. Sodium
- 9. Potassium
- 10. Protein

Samples of plasma were kept at circa 4°C and assays carried out within 24 h of sampling on those parameters which may have proved unstable if retained for longer. If insufficient sample was obtained for all assays to be carried out, preference was given in the numbered order.

Urinalysis

Collection of individual urine samples were made from the same animals used for the haematology bleed, after dosing the mice with 0.5 ml of distilled water. The collection was over a 4 h period of food and water deprivation during Week 13 of dosing.

The following measurements were carried out:-

Glucose
Blood
Volume
Protein
Ketones
Bile pigments
Colour
pH
Specific gravity
Microscopic examination of the spun deposit.

Pharmacokinetic Sampling

During the terminal necropsies blood samples and stomach contents were taken from 5 mice selected at random from each group where possible. It was necessary with female animals receiving 250 mg HMX/kg/day to retain any excess sample remaining after completion of clinical chemistry analyses due to the low survival rate.

Whole blood was taken into heparin and the plasma deep frozen after separation by centrifugation from the red cells. Stomach contents were taken into glass bottles and deep frozen.

Termination

All animals which died or were killed were necropsied. The gross dissection and evaluation was performed by or under the supervision of the pathologist allocated to the experiment. The necropsy was defined as external examination, including body orifices and examination and fixation of all the following tissues.

Adipose tissue (perirenal) Mesenteric lymph node Adrenals Nasal turbinate Aorta Ovaries Bladder Pancreas Brain Parathyroids Bronchial lymph node Pituitary Caecum Prostate Colon Rectum Duodenum Salivary gland (submaxillary) Eyes Sciatic nerve Fallopian tubes Skin (abdominal) Femoral bone smear Spinal cord Gross lesions Spleen Heart Sternebrae, (plus marrow) Ileum Jejunum Submaxillary lymph node Kidneys Testes Liver Thigh muscle Lumbar, sacral and dorsal Thymus ganglia Thyroids Lungs Trachea Mammary gland Uterus

Femoral bone marrow smears were prepared from all animals at death, air-dried and fixed in absolute methanol for at least 5 min.

All tissues and/or organs were examined in situ, then dissected from the carcass, re-examined, including cut surfaces, and fixed in 10% neutral buffered formalin (except eyes which were preserved in Davidson's fluid).

Lungs were fixed in their entirety after opening and examining the trachea and mainstem bronchi.

The calvarium was removed and the dorsal nasal bone removed for examination of nasal turbinates.

Other tissues were fixed after slicing to a thickness not exceeding 5 mm.

Distended urinary bladders were opened and examined before fixation. Contracted, empty bladders were partially distended with formalin and opened and examined after fixation.

Liver lobes were sliced, the kidneys cut transversely and the cut surfaces examined before fixation.

The entire mucosal surfaces of the oesophagus, stomach, small and large intestines and rectum were opened and examined before fixation.

Several thoraco-lumbar vertebrae were fixed with the spinal cord in situ.

All gross lesions were recorded in narrative, descriptive terms, including location, size (in mm), number, shape, colour and texture.

Carcasses of animals were discarded immediately following autopsy and fixation of all tissues listed above.

Processing of Fixed Tissues

The fixation times were no less than 48 h and not more than 12 weeks.

Tissues were trimmed to a maximum thickness of 3 mm for processing.

Parenchymal organs, e.g. liver, were trimmed to allow the largest surface area possible for examination.

Mid-transverse sections through the entire cortex and medulla of each kidney were submitted.

Entire coronal (a transverse section parallel to the long axis of the body) sections of both right and left lungs including main-stem bronchi were submitted.

The spinal cord was sectioned in the thoraco-lumbar region.

Three cross sections of brain included (a) frontal cortex and basal ganglia, (b) parietal cortex and thalamus, and (c) cerebellum and pons.

Hollow organs were trimmed and blocked to allow a cross section slide from mucosa to serosa.

Histological Technique

Tissues were cut at 4-6 μm thickness and stained with haematoxylin and eosin (H & E).

Histopathological Examination

All male animals in the control group and those receiving 30 or 75 mg HMX/kg/day were examined histopathologically. Female control mice and those receiving 30 or 90 mg HMX/kg/day were similarly examined. In addition, the liver, kidneys, spleen and brain from all other animals were examined. At the Sponsor's request, groups showing extensive mortality were not examined histopathologically.

Histopathological examination was defined as histological examination of the following:

Adrenals Aorta Bladder Brain (3 sections including frontal cortex and basal ganglia, parietal cortex and thalamus and cerebellum and pons) Bronchial lymph node Fallopian tubes (where possible) Gross lesions Heart Kidneys Large intestine (caecum, colon, rectum) Liver Lungs Mammary gland Mesenteric lymph node Muscle (thigh) Nares Oesophagus

Ovaries Pancreas Perirenal fat Pituitary Prostate Salivary gland (submaxillary) Sciatic nerve Skin Small intestine (duodenum, jejunum, ileum) Spinal cord (thoracolumbar) Spleen Sternebrae (including marrow) Stomach (glandular and nonglandular) Submaxillary lymph nodes Testes Thymus Thyroids (with parathyroids where present on section) Trachea Uterus

Statistical Evaluation

Analysis of mortality was carried out using Fisher's exact probability test. Other parameters were investigated for statistically significant differences by the application of analysis of variance deriving t values from standard deviations. Males were treated independently of females. The level of probability chosen as significant was P 0.05, but the actual levels are reported.

RESULTS

Dosing commenced: 16 January 1981
Duration of dosing: 95 days minimum
Termination: 21-23 April 1981

Observations

Mortality

There were 50 premature decedents during the study, distributed as follows:

	Dos	e L		Male mg		kg/day	Dos	e Le		male	s IMX/kg	/day
	0	5	12	30	75	200	0	10	30	90	250	750
No. of Deaths	0	0	0	1	2	***	1	0	1	0	** 12	*** 20

Asterisks indicate degree of significance in accordance with Fisher exact probability test.

** = P<0.01 *** = P<0.001

Circumstances of death for each premature decedent are given in Appendix 13.

Clinical Signs

Compound Related Signs

Male animals receiving 75 or 200 mg HMX/kg/day and female mice receiving 250 or 750 mg HMX/kg/day appeared slightly more active than other groups during Weeks 12 and 13 of treatment. Female mice receiving 750 mg HMX/kg/day were more excitable and 'jumpy' from Week 4 to Week 7 of dosing.

Incidental Findings

No other clinical signs were noted which could be attributed to dosing with HMX. The only other clinical signs seen were, for example, bald patches, sparse hair growth and damaged or missing tail tips, distributed throughout the dose groups. These are common occurrences in laboratory mice.

Body Weights

Group mean body weights are presented numerically in Table 1 and graphically in Figures 1 and 2.

Dosing with HMX appeared to have little effect on the body weight of male or female mice.

Male mice receiving 75 mg HMX/kg/day showed a slightly increased body weight gain when compared with control male mice. The effect appeared most marked over Weeks 5 and 6 of treatment where statistical significance of P<0.001 and P<0.01 respectively was achieved. Over the period of treatment a 6% increase in weight gain compared with that of controls was seen in these mice.

Female mice receiving 250 mg HMX/kg/day achieved an 11% increase in bodyweight gain compared with female control mice. The increase was statistically significant only during Week 11 of dosing (P<0.05).

Statistically significant increases in body weight were occasionally noted in other dose groups early and late in the study, but no other consistent trends were noted.

Food Consumption

Group mean food consumption is presented numerically in Table 2.

Male mice receiving 75 or 200 mg HMX/kg/day showed reduced food consumption over the study period, eating 14% or 19% less food than control males respectively.

Female mice receiving 750 mg HMX/kg/day ate slightly less than female control mice (9% reduction over 13 week period). Data for the final weeks of the study may be distorted by the small number of surviving mice receiving 750 mg HMX/kg/day.

Water Consumption

Visual assessment of water intake for each mouse during treatment revealed no intergroup differences.

Achieved Dosage

Group mean values for achieved dosage are presented in Table 3.

The variation in food consumption which occurred during the treatment period resulted in some deviation of weekly achieved dosages from theoretical values, but over the whole treatment period the values are considered to be within acceptable limits.

Diet Analysis

Results of the analysis of diet for HMX concentration are given in Table 4. Methodology of analysis is given in Appendix 14.

Values obtained for the analyses were generally very acceptable, although 5 deviations outwith a 10% limit were obtained. These deviations occurred in the lowest dose groups in all cases but one, and as the theoretical concentrations of HMX in these batches of diet were very low, even a small deviation from theoretical concentration in terms of ppm produced a large % error. The accuracy of formulation and analysis was therefore not felt to be a problem overall.

Ophthalmoscopy

No lesions were observed which could be attributed to dosing with HMX. In 3 animals (2 males receiving 30 mg HMX/kg/day and one control female) during Week 13, the eyelids of the right eye were closed, but this was attributed to damage caused by orbital sinus bleeding.

Laboratory Investigations

Haematology

Group mean values are presented in Tables 5 and 6 and individual values in Appendices 3 and 4. Analyses were carried out during Week 12 of dosing.

Males: No dose related trends were noted between control groups and those receiving HMX and all values fell within expected ranges. Statistically significant differences were occasionally obtained in PCV, MCH, MCV and HepatoQuick time, but these were felt to be due to data structure and not of biological significance. Heinz body preparations were all negative.

Females: All values fell within expected ranges. A slight fall in haemoglobin concentration was noted between controls and mice receiving 750 mg HMX/kg/day, but although this was slightly statistically significant (P<0.05) it was felt to be of little biological

significance, particularly in view of the small sample size at 750 mg HMX/kg/day (3 samples only were obtained). A slight increase in WBC count was noted at 750 mg HMX/kg/day (P<0.05). This was caused largely by a slight increase in lymphocyte numbers at this dose level (P<0.01). As with male mice, other statistically significant events were thought to be due to data structure and not biologically significant. All Heinz body preparations were negative.

Clinical Chemistry

Group mean values are presented in Tables 7 and 8 and individual values in Appendices 5 and 6. Analyses were carried out on samples obtained at termination.

Males: BUN values for animals receiving 75 or 200 mg HMX/kg/day were slightly depressed but values remained within expected ranges.

Glucose concentration in the blood of animals receiving 200 mg HMX/kg/day was reduced compared with controls. Wide variation in glucose concentration was apparent in all groups. ALT and AP values were slightly depressed in animals receiving 200 mg HMX/kg/day compared with control males.

Levels of LDH showed wide variation within all groups. Statistically significant reductions in total protein, albumin and A/G ratios were observed in animals receiving 75 mg HMX/kg/day. The A/G ratio of animals receiving 200 mg HMX/kg/day was also slightly reduced compared with controls.

Females: Mice receiving 250 mg HMX/kg/day showed a slight reduction in AP level compared with control mice. As with male mice, wide variation in LDH values was apparent in all groups.

A statistically significant elevation of albumin concentration was seen in mice receiving 30 mg HMX/kg/day.

Urinalysis

Group mean values are presented in Tables 9 and 10 and individual values presented in Appendices 7 and 8. Urinalysis was carried out during Week 13 of treatment.

Males: Despite water-loading the mice with water at a rate of 0.5 ml/animal, the success rate of urine collection from control animals and those receiving 30 mg HMX/kg/day was low so that comparisons between control and dosed groups cannot readily be made.

Animals receiving 200 mg HMX/kg/day appeared to produce a more acidic urine than control mice. A slight reduction in S.G. was noted with increasing dose level.

Females: A slight increase in SG was noted in animals receiving 250 mg HMX/kg/day compared with controls. This increase was mainly due to the values obtained from 2 mice.

Terminal Studies

Organ Weights

Group mean values are presented in Tables 11-14 and individual results in Appendices 9-12.

Males: A slight increase in absolute brain weight was noted in animals receiving 200 mg HMX/kg/day compared with controls. This was statistically significant to P<0.001. Occasional incidences of statistical significance were seen in kidney and testes weights, but without distinct trend.

Brain weight relative to body weight was also slightly increased in mice receiving 200 mg HMX/kg/day compared with controls (P<0.05). Relative testes weights were marginally decreased at 12 mg HMX/kg/day (P<0.05) or 30 mg HMX/kg/day (P<0.01).

Females: Absolute brain weight of female mice receiving 250 mg HMX/kg/day was slightly increased when compared with control mice (P<0.01). A minor decrease in kidney weight (at 90 mg HMX/kg/day) and a slightly reduced spleen weight (at 250 mg HMX/kg/day) were also noted. Relative spleen weight was decreased at 250 mg HMX/kg/day compared with controls (P<0.01).

Gross and Histopathology

Gross pathology and histopathology findings for individual animals are presented in Appendix 13.

There were no dose related findings in this study. Three animals (one male receiving 75 mg HMX/kg/day and one female in each of the groups receiving 10 or 90 mg HMX/kg/day) had cysts in the brain, and one female animal at 30 mg HMX/kg/day had a cyst in the spinal cord.

DISCUSSION

Despite the relatively high mortality rates at higher dose levels of HMX, little evidence of toxic changes could be found with the investigations carried out.

There was a subjective view that male and female mice at each of their 2 highest dose levels were more excitable than their companions, but this trend was largely masked by the general excitability of the strain of mouse used.

No marked effect on body weight was seen in male or female mice, but reduced food consumption was noted in male mice at the 75 or 200 mg HMX/kg/day dose levels and in female mice at 750 mg HMX/kg/day. This suggests that these mice may have been converting food more efficiently than control mice.

Laboratory investigations were limited by the low survival rate at the high dose level in female mice. Only 3 samples from mice receiving 750 mg HMX/kg/day were received for haematology and there were no samples from these mice for clinical chemistry or urinalysis. However, none of the effects in haematology, clinical chemistry or urinalysis were sufficiently marked to give any indications as to the cause of deaths.

Male mice receiving 200 mg HMX/kg/day showed a slight increase in absolute brain weight, and in brain weight relative to body weight. Female mice also showed a slight increase in absolute brain weight at the 250 mg HMX/kg/day dose level. Interpretation of these findings is made difficult by the containment of the brain within rigid boundaries. Female mice receiving 250 mg HMX/kg/day also showed a slight reduction in absolute and relative splenic weights, but the significance of these findings is unclear. It should be noted that comparison of the organ weights of female mice receiving 750 mg HMX/kg/day with those of control mice cannot readily be made, as none of these mice survived to termination and almost all were found dead, allowing autolysis to commence prior to autopsy. process may have affected the organ weights, as autolytic changes were seen in some of the tissue sections from these animals.

The cysts seen in the brain or spinal cord of 4 animals on study were thought to be unrelated to dosing with HMX. These lesions have been documented in man and have been seen in rats and mice, generally as incidental findings.

The deaths which occurred at 30 mg HMX/kg/day in both sexes were thought unrelated to dosing with HMX. The circumstances of death of 2 male animals receiving 75 mg HMX/kg/day do not reveal the likely cause of death.

CONCLUSION

Dosing of B6C3F1 mice for 13 weeks with dietary concentrations of HMX at 200 mg/kg/day (males) and 250 or 750 mg/kg/day (females) resulted in greatly increased numbers of deaths. Only minor changes of doubtful significance, were identified in the observations made (e.g. increased brain weight in top dose males and females). None was sufficient to offer an obvious explanation for the deaths.

REFERENCE

1. Zimmerman, H.M. and Innes, J.R.M. (1979), Pathology of Tumours in Laboratory Animals, WHO Vol. 2 p.p. 632.

TABLE 1

HMX: 13 Week Toxicity Study in Mice Body Weights: Group Mean Values (q)

				ă	se Group	/Dose Le	Dose Group/Dose Level (mg/kg/day)	kg/day)	<u> </u> 			
Treatment Period	13	2.5	33	4.5	5\$	6.5	18	28	38	48	85	89
	0	\$	12	30	75	200	0	10	30	90	250	750
0	19.520	19.920	20.420	20.120	20.320	20.220	17.120	16.920	17.220	17.020	17.520	17.320
0 Day 4	20.8			8.02	9.02		17.4			17.7	17.4	
-	21.7	21.9	22.1	21.8	21.7	20.819	18.1	18.6	19.10	18.4	17.9	17.818
1 Day 4	22.3	22.2	22.5	22.3	21.8	21.516	18.6	18.5	19.5	18.8	18.2	18.512
~	22.8	22.8	23.0	22.7	22.9	22.814	19.1	9.61	20.2	19.3	19.4	20.413
2 Day 4	23.5	23.5	23.3	23.0	23.4	22.9	20.0	20.2	9.02	19.9	19.8	
٣	23.8	23.9	23.7	23.5	23.6	23.513	9.02	20.9	21.3	20.7	20.219	
3 Day 4	23.9	24.1	24.4	23.8	24.119	24.5	21.2	21.5	21.9	21.2	20.4	20.7
•	23.8	24.0	24.6	24.2			21.9	21.8	22.0	21.7	21.318	21.4
\$	24.0	24.4	24.8	24.6			22.0	21.9	22.6	51.9	21.9	21.9
9	24.7	24.9	25.4	24.9	26.1		22.5	22.6	22.819	22.7	22.9	22.2
_	25.5	25.3	25.7	25.2	26.5*	26.0 9	23.6	23.3	23.8	23.4	23.4	23.0 7
80	25.8	25.6	25.9	25.7	26.9*	26.68	23.6	23.7	24.3	23.8	23.8	23.1
•	26.0	25.9	26.5	26.1	27.0*	26.9 7	24.0	23.9	24.0	23.5	24.015	23.8
10	9.92	26.8	27.1	26.5	27.6	27.3	24.1	23.7	24.4	23.5	23.810	23.7 3
	26.9	17.1	7.72	26.9	27.6	26.7	24.919	25.2	25.1	24.5	25.8	24.3
12	27.5	27.72	28.0	27.2	28.4	27.3	25.1	25.3	25.3	24.7	26.0 8	25.3
13	27.5	27.9	28.2	27.7	28.8*	27.6	25.1	25.2	25.7	25.1	26.4	ı
Total weight gain Weeks 0-13*	8.0	8.0	7.8	7.6	8.5	7.4	(8.01)	8.3	8.5	8.1	8.9	8.01
• of Controls	•	001	86	95	106	66	-	104	106	101	m	100
				-								

t = weight gain to week 12 for Groups 1 and 69.

Figures in superscript denote numbers of animals from which data derived.

* = Significantly different from control, P<0.05
** * Significantly different from control, P<0.01

••• = Significantly different from control, P<0.001

TABLE 2

HMX: 13 Week Toxicity Study in Mice Food Consumption: Group Mean Values (q/Mouse/Week)

				Dog	se Group	/Dose Le	Dose Group/Dose Level (mg/kg/day)	kg/day)				
Treatment Period	13	23	3&	43	5ď	€₫	19	29	3\$	ð.Þ	6 5	89
	0	5	12	30	75	200	0	10	30	06	250	750
1	4920	5220	5120	4220	4620	4519	4820	5620	5420	5820	61092	6019
7	54	59	55	48		4414	20	53	48	a47	4420	
٣	5.4	49	a ₅ 7	99 _e	54	4513	55	64	64	b6419	6919	
4	62	62	09	59	5218	4112	65	9	99	6620	99	63
Ŋ	69	64	69	89	58	5811	72	69	89	69	6418	99
9	74	70	73	7.0	55	5710	74	99	6919	73	7.0	67
7	89	64	99	62	58		65	65	63	62	65	26 8
80	63	59	61	62	55	52 8	63	62	65	62	61	57 7
6	59	61	99	61	99	63 7	29	63	63	62	6215	62 4
10	59	9	54	55	51	20	59	63	29	64	6311	56 3
11	55	09	58	b ₅₅ 19	50	47	6219	89	89	65	6810	61
12	57	57	59	5220	20	40	63	99	58	61	8 95	
13	54	61	52	20	41	36	63	65	99	99	58	d45 0
Total eaten (g) Weeks 1-13	ררר	783	781	750	899	632	908	825	819	819	800	735
% of Controls	•	101	101	16	86	81	-	102	102	102	66	91

a = animals had flooded cages ~ food consumption measured over part week

b = food left not recorded

c = omitted from mean due to erroneous data

 $d = food\ consumption\ calculated\ over\ fraction\ of\ week\ for\ 3$ animals

Figures in superscript indicate numbers of animals from which data derived

TABLE 3

HMX: 13 Week Toxicity Study in Mice Achieved Dosage: Group Mean Values (mg/kg/day)

			Doo	se Group	Dose Group/Dose Level (mg/kg/day)	el (mg/kg/	'day)				
Treatment Period (weeks)	2.5	33	43	53	6ئ	. •	28	3\$	48	58	. 59
	2	12	30	75	200		10	30	06	250	750
	.2	12	24	7.1	207		10	29	96	281	1052
2	9	13	35	69	661		0 0	27	17	194	477
3	2	13	43	93	509	_	12	39	1117	373	1136
4	9	13	36	98	183		12	37	110	291	964
2	2	14	33	84	279			32	001	258	821
9	9	13	32	92	228			32	66	265	794
7	2	12	27	78	193	_	10	27	79	222	625
80	4	11	28	69	187		6	59	82	229	682
6		12	30	75	235		10	29	06	260	816
10		10	27	29	175	_	10	31	95	258	733
	- 2	11	27	72	184		11	31	9.5	264	9//
12	<u>د</u>	13	28	74	165	_	0	27	98	216	538
13	2	11	27	62	154		0	30	93	231	1
Mean achieved dosage	5.2	12.2	30.5	75.1	199.8	16	10.5	30.8	93.1	257.1	B784.5
% of Nominal	104	102	102	100	100	105	51	103	103	103	105

a = mean derived from 12 values only

TABLE 4a

HMX: 13 Week Toxicity Study in Mice Analysis of Diet for HMX

Male Dosed Groups

Date of Sampling	Dose Group	Theoretical Conc. (ppm)	Mean Observed Conc. (ppm)	Deviation of Observed from Theoretical (%)
16 Jan.	2 3*	14	14	0.0
1981	33	35	32	8.6
Week 1	43	84	79	6.0
	5♂	225	232	3.1
	63*	662	657	0.8
23 Jan.	23	16	16	0.0
1981	33	39	39	0.0
Week 2	43	113	113	0.0
l	53	257	274	6.6
	63	688	708	2.9
30 Jan.	25	15	14	6.7
1981	3 3	38	39	2.6
Week 3	43	105	102	2.9
	53	280	276	1.4
	6ਤੋਂ	756	754	0.3
6 Feb.	23	16	17	6.3
1981	33	37	36	2.7
Week 4	43	102	111	8.8
	53*	282	270	4.3
	63	747	719	3.7
27 Feb.	2 3*	13	13	0.0
1981	3♂	31	35	12.9
Week 7	43	76	78	2.6
,	5ਰੰ	248	250	0.8
	63	645	623	3.4

TABLE 4a (continued)

Date of Sampling	Dose Group	Theoretical Conc. (ppm)	Mean Observed Conc. (ppm)	Deviation of Observed from Theoretical (%)
20 March	23	15	18	20.0
1981	33	35	37	5.7
Week 10	43	89	94	5.6
week 10	5 3*	254	266	4.7
	63	661	679	2.7
10 April	23	16	16	0.0
1981	33	41	38	7.3
Week 13	43	105	109	3.8
Week 13	53	302	301	0.3
	6₃*	830	874	5.3

TABLE 4b

Female Dosed Groups

Date of Sampling	Dose Group	Theoretical Conc. (ppm)	Mean Observed Conc. (ppm)	Deviation of Observed from Theoretical (%)
16 Jan.	2♀	23	28	22.0
1981	3♀	68	62	8.8
Week 1	42	204	195	4.4
	5♀	578	595	2.9
	6₽	2146	2109	1.7
23 Jan.	2♀	25	25	0.C
1981	3♀	78	79	1.3
Week 2	4 🕯	201	205	2.0
week £	5 ⊋	575	569	1.0
	65	1753	1726	1.5
30 Jan.	2♀	26	28	7.7
1981	3⊋	90	92	2.2
Week 3	42	258	257	0.4
week 5	5⊋	754	750	0.5
	63	2650	2781	4.9
6 Feb.	23	27	25	7.4
1981	3♀	85	87	2.4
Week 4	43	247	243	1.6
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	54	642	622	3.1
	63	2228	2279	2.3
27 Feb.	2♀	24	27	12.5
1981	3.2	70	70	0.0
Week 7	4.2	204	208	2.0
	53	613	624	1.8
	63	1787	1788	0.1

TABLE 4b (continued

Date of Sampling	Dose Group	Theoretical Conc. (ppm)	Mean Observed Conc. (ppm)	Deviation of Observed from Theoretical (%)
20 March	2♀	27	26	3.7
1981	3♀	79	84	6.3
Week 10	4♀	238	231	2.9
	5⊋	685	693	1.2
	6₽	2204	2190	0.6
10 April	29	27	31	14.8
1981	3♀	82	82	0.0
Week 13	4 ♀	245	236	3.7
	5♀	728	749	2.9
	6.5	2550	2531	0.7

TABLE 5

HMX: 13 Week Toxicity Study in Mice

Haematology: Males

Group Mean Values

Dose mg/kg /day	Tests Units	нь 9./100 m1	RBC	₹ ≈	RUE EX	MCV f1	M/HC 9/d1	Reti 8	WBC	Neut	duuk' j	Mono	Eos	Hepa Sec
Con	Numbr Mean S.D.	10 16.5 0.6	10 8.4 0.3	10 47	10 20 0	01 9 ²	10 35 1	1.6	10 6.2 1.6	10 1.1 0.5	10 5.0 1.3	10 0.1 0.1	10 0.0 0.1	10 21.9 0.9
30	Numbr Mean S.D. Sig	10 16.3 1.7	10 8.1 0.9	10 48 1	10 20 0	09 8 8	10 34	10 1.6	10 6.2 1.6	1.1	10 5.0 1.4	10 0.1 0.1	10 0.0 0.1	20.9
75	Numbr Mean S.D.	16.6	10 8.2 0.4	10 49 49	10 20 1	100	10 34 34	1.3	10 7.3 1.2	1.2	10 6.1 1.1	10 0.0 0.1	10 0.0 0.0	21.4
200	Numbr Mean S.D. Sig	6 16.6 0.4	6 8.2 0.3	6 48 1	50 20 0	6 59 1	35 15	6 1.2 0.5	6.1 1.4	6 1.0 0.4	6 5.1 1.1	6.0 0.1	0.0 0.0	21.12

For remaining units see Appendix 15

= Significantly different from control, P<0.05

** = Significantly different from control, P<0.01

TABLE 6

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HMX: 13 Week Toxicity Study in Mice
Haematology: Females

Group Mean Values

Heba Sec	10 22.7 2.4	10 22.0 1.6	10 21.9 1.0	8 22.0 0.8	3 21.4 0.3
Sog	0.0 0.0	10 0.0 0.0	0.0	8 0.1 0.0	0.0
Mono	0.1 0.1 0.1	0.0	0.1 0.1 0.1	0.1 0.1	0.1 0.0
Cymp.	10 4.1 1.3	10 4.3 1.5	10 4.4 1.4	4.7 0.7	3 6.6 1.7 **
Neut	10 0.8 0.4	10 0.8 0.4	10 0.7 0.3	0.8 0.3	3 0.9 0.3
MBC .	10 5.0 1.7	10 5.1 1.6	10 5.2 1.7	8 5.6 0.9	3 7.5 1.7
Reti	10 1.0 0.5	10 1.4 0.4	10 1.2 0.3	8 1.1 0.4	3 1.2 0.2
MCHC 9/d1	10 35	10 35 1	10 35 1	8 * * *	* 133 * 133
MCV F1	10 58 2	10 57 3	10 57 2	8 90 3	39 59 5
¥ E E	10 21 1	10 20 1	10 20 1	8 70 1	61 1 *
D ∞	10 48 2	10 47 1	10 48 1	8 4 1	3 49 2
RBC	10 8.3 0.3	10 8.3 0.6	10 8.4 0.3	8.2 0.5	8.3 0.8
Hb 9/100 m1	10 17.1 0.8	10 16.7 0.4	10 16.8 0.7	8 16.5 0.7	3 16.1 0.9
Tests Units	Numbr Mean S.D.	Numbr Mean S.D. Sig	Numbr Mean S.D. Sig	Numbr Mean S.D. Sig	Numbr Mean S.D. Sig
Dose mg/kg /day	r <mark>o</mark>	30	06	250	750

For remaining units see Appendix 15

* = Significantly different from control, P<0.05

** = Significantly different from control, P<0.01

TABLE 7

HNX: 13 Week Toxicity Study in Mice Clinical Chemistry: Males

				ÿ	W dno	Mean V	alues					
Dose all kg	Tests Units	FILTN mmo1/	Glu mmol/	AST ALT 10/1 10/1	ALT IU/1	AP [1] /1	1,0H	N.a. mmol/	K mmol/ 1	îгр 9/1	Altb 9/1	AG-R
Con	Numbr Mean S.D.	9 10.6 1.6	9 11.34 5.70	65	2 % 4	9 2002	10 645 354	9 165	9 11.0 2.5	8 55 2	9 8 1	8 1.5 0.1
30	Numbr Mean S.D. S19	10 9.9 1.8	10 10.41 4.32	10 50 8	10 24	10 201 17	10 470 172	164	10.7	9 2,2	10 32 1	9 2.1 0.1
75	Numbr Mean S.D. Sig	10 8.0 1.5 **	10.92 4.46	8 20 20	10 27 7	10 147 197 30	10 6 38 281	159	11.2	10 51 3	10 20 10 11	1.4
500	Numbr Mean S.D. S1g	8.1 8.0 8.4	7. 19 3. 98	92 92 93	9 70 8	, 180 50	896 896 397	6 168 13	11.7	5 56 6	6 32 3	5. 1.2 0.1

^{* =} Significantly different from control, P<0.05

^{** =} Significantly different from control, P<0.01

^{*** =} Significantly different from control, P<0.001

TABLE 8

HMX: 13 Week Toxicity Study in Mice Clinical Chemistry: Females

				3			7-1	,				
Dose mg/kg /day	Tests Units	BCN GI minol/min	Gla , mmol/ l	AST 10/1	Sroup r AST ALT IU/1 IU/1	AP IU/1	values IDH 1	N3 mmol//	K nomol/ 1	97.9	A1b g/1	AG-R
Con	Numbr Mean S.D.	8 10.5 12. 2.2 5.	12.50 5.99	10 62 17	10 21 11	337	9 628 231	2 158 8	2 10.0 1.6	60	34	1.4
30	Numbr Mean S.D.	9 8 12.7 12.65 2.8 7.42	8 65 42	9 58 21	9 28 12	307	9 746 451	170	4 12.1 3.5	63	36	8 1.3 0.1
06	Numbr Mean S.D.	10 1 9.9 12. 2.0 4.	10 12.62 4.31	10 66 22	10 26 6	10 329 30	10 763 319	167	10.4	10 61	10 35 1	10 1.4 0.1
250	Numbr Mean S.D. Sia	10.0 13.45	45	7 58 12	7 23 8	772 24	7 691 282	1 167	8.7	95°°	33 1	1.3 0.1

* = Significantly different from control, P<0.05

** = Significantly different from control, P<0.01

TABLE 9

HMX: 13 Week Toxicity Study in Mice Urinalysis: Group Mean Values - Males

Dose (mg/kg/day)		Нď	SS	Vol (m1)
Control	Mean S.D.	8.0 ² 0.0	1.033 4	0.8 ² 0.4
30	Mean S.D.	ı	1.028 2 0.018	•
75	Mean S.D.	8.1 ¹⁰	1.018 ¹⁰	0.79
200	Mean S.D.	6.9 7	1.014 7	0.67

- = no data available

Figures in superscript indicate numbers of animals from which data derived

= Significantly different from control, P<0.05

** = Significantly different from control, P<0.01

TABLE 10

HMX: 13 Week Toxicity Study in Mice Urinalysis: Group Mean Values - Females

Dose (mg/kg/day)		Нd	SS	Vol (m1)
Control	Mean S.D.	8.0	1.018	0.9
30	Mean S.D.	8.4	1.018	0.9
06	Mean S.D.	8.4	1.018	0.7
250	Mean S.D.	8.0 0.8	1.0239	0.79

Data derived from 10 animals unless otherwise stated in superscript

* = Significantly different from control, P<0.05

** = Significantly different from control, P<0.01

TABLE 11

HMX: 13 Week Toxicity Study in Mice Absolute Organ Weights (q) Group Mean Values - Males

Dose Lavel/ (mg/kq/day) /Sex		Body Weight (q)	Brain	Heart	Kidneys	Liver	sbung	Spleen	Testes
٥٠	Mean S.D.	26.3 ²⁰	0.020	0.156	0.272	1.324	0.175	0.064	0.177
53	Mean S.D.	27.2 ²⁰	0.449	0.153	0.278	1.363	0.179	0.065	0.177
123	Mean S.D.	27.4 ²⁰ 1.8	0.453 ¹⁹	0.154	0.286*	1.335	0.186	0.061	0.180
303	Mean S.D.	26.6 ¹⁹ 1.7	0.45618	0.154 ¹⁹	0.277 ¹⁹	1.315 ¹⁴ 0.167	0.171 ¹⁹	0.063 ¹⁹	0.173 ¹⁹
753	Mean S.D.	28.1 1.2	0.468 ¹⁸	0.159 ¹⁸ 0.016	0.283 ¹⁸ 0.025	1.363 ¹⁸ 0.077	0.179 ¹⁸	0.062 ¹⁸	0.18518
2003	Mean S.D.	26.9 ⁷ 1.6	0.483 7	0.149 7	0.269 ⁷ 0.027	1.324 7	0.189 7	0.061 7	0.178 7

Data derived from 20 animals unless otherwise stated in superscript

^{* =} Significantly different from control, P<0.05

^{** =} Significantly different from control, P<0.01

^{*** =} Significantly different from control, P<0.001

TABLE 12

HMX: 13 Week Toxicity Study in Mice Organ Weights as % of Body Weight Group Mean Values: Males

	Body Weight (9)	Brain	Heart	Kidneys	Liver	Lungs	Spleen	Testes
Mean S.D.	26.3 ²⁰	1.72	90.0	1.03	5.04	0.08	0.25	0.69
Mean S.D.	27.2 ²⁰	1.67	0.56	1.02	5.04	0.09	0.24	0.66
Mean S.D.	27.4 ²⁰	1.66 ¹⁹ 0.11	9.56	1.04	4.87	0.69	0.22	0.65*
Mean S.D.	26.6 ¹⁹	1.72 ¹⁸	0.57 ¹⁹	1.04 ¹⁹	4.94 ¹⁹ 0.47	0.6419	0.23 ¹⁹	0.6419
Mean S.D.	28.1 ¹⁸	1.67 ¹⁸	0.5718	1.00 ¹⁸	4.85 ¹⁸ 0.29	0.65 ¹⁸	0.22 ¹⁸ 0.05	0.66 ¹⁸ 0.06
Mean S.D.	26.97	1.83 7	0.56 7	7 66.0 0.07	4.91 7	0.70 7	0.23 7	0.66 7

* = Significantly different from control, P<0.05

^{** =} Significantly different from control, P<0.01

TABLE 13

HMX: 13 Week Toxicity Study in Mice Absolute Organ Weights (q) Group Mean Values: Females

					ı			
Dose Level (mg/kq/day) /Sex		Body Weight (g)	Brain	Heart	Kidneys	Liver	Lungs	Spleen
&0	Mean S.D.	24.2 ¹⁹	0.461 ¹⁹	0.139 ¹⁹	0.192 ¹⁹ 0.017	1.289 ¹⁹ 0.123	0.186 ¹⁹	0.085 ¹⁹
¿01	Mean S.D.	24.2	0.463	0.141	0.193	1.291	0.020	0.086
₹0£	Mean S.D.	24.8 ¹⁹	0.467 ¹⁹	0.142 ¹⁹	0.198 ¹⁹ 0.014	1.339 ¹⁹ 0.104	0.189 ¹⁹	0.089 ¹⁹
ځ0 6	Mean S.D.	23.9	0.466	0.133	0.184*	1.312	0.181	0.085
2509	Mean S.D.	25.4 8	0.491 8	0.140 8	0.195 8 0.013	1.386 8 0.212	0.178 8	0.078 8

Data derived from 20 animals unless otherwise stated in superscript

^{* =} Significantly different from control, P<0.05

^{** =} Significantly different from control, P<0.01

TABLE 14

HMX: 13 Week Toxicity Study in Mice Organ Weights as % Body Weight Group Mean Values: Females

Dose Level (mg/kg/day) /Sex		Body Weight (q)	Brain	Heart	Kidneys	Liver	Lungs	Spleen
¿0	Mean S.D.	24.2 ¹⁹ 1.0	1.92 ¹⁹ 0.08	0.58 ¹⁹	0.81 ¹⁹ 0.06	5.33 ¹⁹ 0.36	0.77 ¹⁹	0.36 ¹⁹ 0.05
\$01	Mean S.D.	24.2	1.92	0.59	0.79	5.35	0.73	0.35
₹0€	Mean S.D.	24.8 ¹⁹	1.88 ¹⁹ 0.06	0.58 ¹⁹	0.79 0.06	5,39 ¹⁹ 0.36	0.77	0.3519
⊹06	Mean S.D.	23.9	1.96	95.0	0.80	5.48	0.77	0.35
2509	Mean S.D.	25.48	1.93 8	0.55 8	0.79 ⁸ 0.03	5.45 8	0.70 8	0.30

Data derived from 20 animals unless otherwise stated in superscript

^{* =} Significantly different from control, P<0.05

^{** =} Significantly different from control, P<0.01

FIGURE 1

HMX: 13 Week Toxicity Study in Mice Group Mean Body Weights (g) - Males

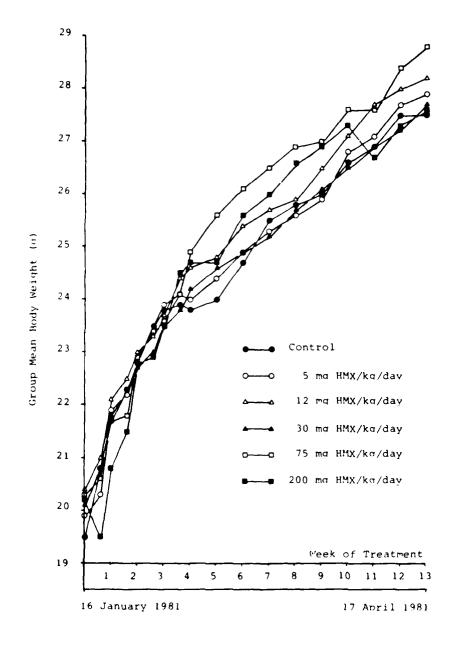
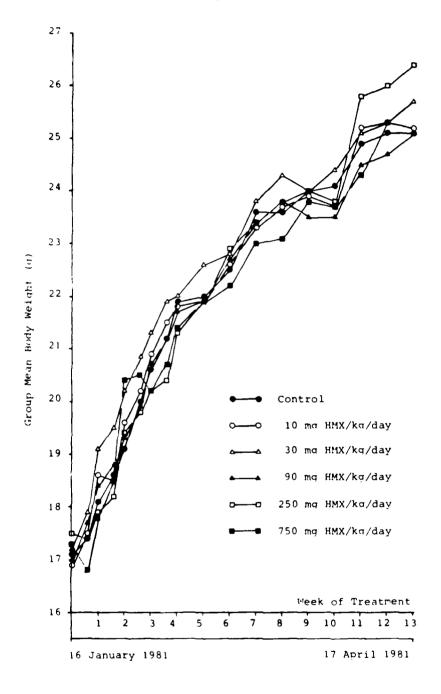


FIGURE 2

HMX: 13 Week Toxicity Study in Mice Group Mean Body Weight (a) - Females



APPENDIX 1

HMX: 13 Week Toxicity Study in Mice Diet Analysis

B.P. NUTRITION (U.K.) LTD.

SPECIAL QUALITY CONTROL OF SMALL ANIMAL DIETS

CERTIFICATE OF ANALYSIS

PRODUCT: RAT & MOUSE NO.1 (MODIFIED) EXPANDED FIRE TOMOGRO-

BATCH NO: 1091

PREMIX BATCH NO P121/128

DATE OF MANUFACTURE: 21	7TH JANUARY 1981
-------------------------	------------------

Nutrient	Found Analys	ıs	Contaminant	Found Analysis		Limit of Detection
Moisture	8.6	0 / ₀	Fluorine	£.2	mg/kg	1.0 mg/kg
Crude Fat	3.€	6,0	Nitrate as NaNO3	7.0	mg/kg	1.0 mg/kg
Crude Protein	15.3	0 /0	Nitrite as NaNO2	2.5	mg/kg	10 mg/kg
Crude Fibre	3.5	* /3	Lead	1.5	mg/kg	0.25 mg/kg
Ach	5.3	e/c	Arsenic	∠ 0.2	mg/kg	0.2 mg/kg
Carrium	0.74	%	Cadmium	0.21	mg/kg	0.05 mg/kg
Phototorus	0.65	0,0	Mercury	40.01	mg/kg	0.01 mg/kg
ម្ចាក	0.16	9/0	Selenium	0.CB	mg/kg	0.02 mg/kg
Chlorine	0.51	°/o			1	
Potassium	6.63	a ′o			ſ	
Magnesium	0.18	0/0	Total Affatoxins 110	NE DETECTE:	Omc3/kg	1 mcg/kg each of
Iron	217	mg/kg			1	B1,E2,G1,G2
Copper	14	mg/kg				
Mar goneso	€3	mg/\g	Total PCB MONE	retrated		0.001 mn/kg
Zinc	46	mg/kg	Total D.D.T.	0.011	mg/kg	0 001 mg/kg 0 001 mg/kg
			Dieldrin	0.001	mg/kg mg/kg	0 001 mg/kg
			Lindane			0.001 mg/kg
			Heptachlor	0.004	mg/kg mg/kg	0.001 mg3.g
			ŕ	0.001	1	0.02 mg/kg
			Malathion	<0.02	mg/kg	002 iligiky
Vitamin A	4750	ıu/kg	Total Viable Organisms 3.	.25 × 10 ³	per grm	1000/g
Vitamin E	85	mg/kg		• • • •		·
Vitamin C		mg/kg	Mesaphilic Spores 15	.0 x 10 ²	per grm	100/9
			Salmonellae Species NON	c petectio	per gim	Absent in
			Presumptive E. coli NON	e detected	per grm	Absent in 10 grm
			E. coli Type 1 NONI	E DETECTED	per grm	Absent in 10 grm
	- 0		Fungal Units NON	E DETECTED	per grm	Absent in
D	DV , .		Antibiotic Activity			10 grm

l'Klopplistone. 23rd Feb 1981

C. R. POPPLESTONE MiSc., Ph.D., C.Chem., M.R.S.C. Quality Control Mariapor

B.P. Nutrition (U.K.) Limited 1 Stepfield, Witham, Essex, CM8 3AB. Telephone: (0376) 513651

APPENDIX 2

HMX: 13 Week Toxicity Study in Mice Water Analysis

nan if nacessavy) H/B/163	1 Mater sain	(miligrammes par intre and millequivalents par intre)	*	THE THE	0,58 Calcium Carbonate	0,50 Calcius Suiphate	05 Magnestus Sulphate 21	0.15 Magnesium Chloride	Sodius Chloride 13	Sodium Nitrate	Potassius Mitrate	Silice	1, Vs Total			This sample is very faint opal in appearance and in free from colour. The rescion is neutral and the water is soft in character sits a low mounts to dissolve and object. The water is from from setals apart from about traces of rinc, from and copper and is of a main factory standard.	Three results indicate from the aspect of the chraical analysis, a wholesome
Ma Lafter fütrat	Read 1- 1 Va	ilre endmil	Anans	ξ	.co.	20.00	5	0					for			ery faint on neutral and lived solids	dicate from
Mineral Analysis of a Sample of Water littration if necessary!	3	imiligrammes par i	: 3	- PE	C		Me 6 06	F 1 0,04					Intel 1, 51	Turner's or the second of the second	Comment	This number is very The reaction is new content of dissolver sinule traces of rich	There regults in

Analysis of Wester

Analys

APPENDIX 2 (continued)

ICLS

H/B/163

Organochlorine Pesticides

alpha - B.H.C.	NDLT 5 ng/l
gamma - B.H.C.	NDLT 5 ng/l
Heptachlor	NDLT 10 ng/l
Aldrin	NDLT 10 ng/l
Dieldrin	NDLT 20 ng/l
p.pD.D.T.	NDLT 10 ng/l

Polynuclear Aromatic Hydrocarbons

Fluoranthene	NDLT	5 ng/1
Benzo (ghi) perylene	NDLT	1 ng/l
Benzo (k) fluoranthene	NDLT	1 ng/1
2,3 o - phenylenepyrene	NDLT	1 ng/1
Benzo (b) fluoranthene	NDLT	1 ng/l
Benzo (a) pyrene	NDLT	1 ng/l
Total PAH	NDLT	10 ng/l

Polychlorinated biphenyls

NDLT 200 ng/l expressed as AROCHLOR 1248

NDLT = Not detected, less than

Signed:

for: I.C.L.S. LABORATORIES LIMITED

APPENDIX 3

HMX: 13 Week Toxicity Study in Mice Haematology: Males

Individual Values

Dose ing/kg /day	Tests Units Grp S Anm	Anm	ИБ 9./100 m.t	RBC	χ ».	M.H.	≯ 1 ±	M (110) q/411	Ret.i	WHY	X ∙ut	сìш⁄: I	Mono	Eos	Hep.
Con	Σ	1 2 20 20 20 20 20 20 20 20 20 20 20 20 2	15.7 17.0 17.1 16.6 16.8 16.8 16.8 16.8 17.9	2	46 48 48 46 46 46 47 47 49 49	2222222222	58 57 58 58 58 58 58	4 x 8 x x x x x x x x	1.6 1.2 2.2 2.0 2.4 0.8 1.0	8.38 8.38 8.39 8.44 8.44 8.99	2.2 1.2 1.4 0.7 0.8 0.8 0.8	0 0 0 4 4	0.0	000000000000000000000000000000000000000	21.2 20.1 20.1 22.3 23.2 23.2 21.7 23.2 22.7 21.7
	Mean S.D.		16.5	8.4	47	0.0	1 95	\$5 1	1.6	6.2 1.6	1.1	5.0	0.1	0.0	21.9
30	Σ	63 64 68 68 68 72 74 75 75	6.66 16.94 16.94 16.94 16.94 18.11 1.81	8.3 8.1 8.7 8.2 9.0 9.0	40 49 48 48 48 51 49 47 47 47	20 20 20 20 20 20 20 20 20 20 20 20 20 2	57 57 58 58 58 58 58 58 58	£ 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	1.2 3.2 0.8 0.8 1.2 1.3 2.4 1.0	5.7 6.2 7.8 7.8 7.8 7.8 7.8	1.1 1.5 1.0 0.8 0.8 1.2 1.2	44.0.6.4.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2	0.1 0.2 0.2 0.1 0.1 0.0 0.0	0.0	20.7 20.7 20.7 22.7 22.7 21.6 22.2 118.9 20.2 20.2
	Mean S.D.		16.3	8.1 0.9	48 1	07	60	34	1.6	6.2	1.1	5.0	0.1	0.0	20.9
1					1 1	9.000				1 1 1	} ! ! ! !	! ! ! !	 	!	!

For remaining units see Appendix 15 # Insufficient blox4 for Retic

APPENDIX 3 (continued)

Doseming kg	Tests Units Grp S Anm	Ę	Htb q 1100 m.t	₩.,	g. ∞	E E	¥.1 +1	4 24€ 9.44€	Reti *	WBC	Neut	qm/s1	Mono	Eos	Hepa Sec
75	x	882 882 883 883 893 893 893	25.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00	2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2	2. 1. 1. 2. 2. 2. 4. 4. 5. 1. 1. 5. 1. 5. 1. 5. 1. 5. 1. 5. 1. 5. 1. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5.	T 2 2 2 2 5 5 2 7 7 7 7 7 7 7 7 7 7 7 7 7	64 53 54 54 54 64 64 61	E	1.3 1.2 1.2 1.2 1.2 1.2 1.2	6.2 7.0 7.1 7.1 7.0 8.9 8.9 8.0 8.0 8.0	0.9 1.8 1.1 0.7 0.9 0.9 1.6	8.7. 6.7. 8.7. 8.7. 7.7. 7.7.	0.0 0.0 0.0 0.0 0.0 0.0	0.0000000000000000000000000000000000000	21.2 20.7 20.8 20.8 20.2 21.2 22.2 20.0 20.0
200	8.70. 8.70. 6.31. 10. 10. 10. 10. 10. 10. 10. 10. 10. 1	101 103 105 109 110	16.6 1.0 16.5 16.5 17.1 16.7 16.8	8.2 7.9 7.9 7.9 7.9 8.0	2 2 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	20 20 20 20 20 20 20 20 20 20 20 20 20 2	25 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	4	2.00 2.00 2.00 4.00 6.00 6.00 6.00 6.00 6.00 6.00 6	7.3 1.2 6.1 3.7 6.2 7.9 6.7	1.1.2	6.1 5.0 3.1 5.7 6.2 6.2 5.3	0.0	0.00	21.4 0.9 0.9 21.2 21.7 20.7 22.2 119.7
	Mean S.D.	; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;	16.6	8.2	48	02	65	35	1.2	6.1	1.0	5.1	0.1	0.0	21.1

For remaining units see Appendix 15

APPENDIX 4

HMX: 13 Week Toxicity Study in Mice Haematology: Females Individual Values

Dose mg/kg /day	Tests Units Grp S Arm	нь 9/100 m1	RBC	£*	<u>\$</u> 8	£1	MCHC g/d1	Reti	WBC	Neut	Сумр	Mono	Eos	Hepa sec
oo oo	1 F 121 124 125 127 127 131 134 136 137 139	16.6 18.5 17.5 17.5 16.9 16.2 16.0 17.1	88.1 88.1 88.1 89.7 99.7 1.9	51 47 47 50 48 48 48 48 48 48 48 48	20 22 23 24 25 25 26 27 27 27 27 27 27 27 27 27 27 27 27 27	62 57 56 56 59 60 57 61 61	33 37 37 38 38 38 38 38 38	2.2 0.6 6.6 0.8 0.8 1.2	0.2.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0	0.4.0000000000000000000000000000000000	41.244.82.22.82	0.00	0000000000	28.7 22.2 21.2 21.3 22.3 22.2 24.7 21.2
	Mean S.D.	17.1	0.3	48	21	58	32	0.5	5.0	0.8	1.3	0.1	0.0	22.7
30	3 F 161 165 165 166 170 170 176 176	16.2 17.2 17.2 16.8 16.8 16.8 17.2 16.6 15.9	7.8 8.6 7.9 7.9 8.0 8.5 8.5	48 47 47 47 49 49 49 46 46	21 20 21 21 20 20 20 20 21 21	62 52 53 54 54 58 58 61	25. 25. 26. 27. 27. 28. 28. 28. 28. 28. 28. 28. 28. 28. 28	4.00 1.00 1.00 1.00 1.00	8 9 8 8 8 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9	0.5 0.5 0.9 0.5 0.5 0.6	2.7.2.2.4.6.2.4.4.8.8.8.4.2.1.8.1.8	000000000000000000000000000000000000000	0000000000	20.2 20.2 20.2 20.2 20.2 20.2 20.2 20.2
 	Mean S.D.	16.7	8.3	47	20 1	57	35 1	1.4	5.1	0.8	4.3	0.0	0.0	22.0

For remaining units see Appendix 15

APPENDIX 4 (continued)

Dose mor/kg /day	Tests Units Grp 3 Anm	Hb 9/100 m1	RBC	F.V.	ACH EQ	MCV f.1	MCHC g/d1	Reti	WBC	Neut	cjmy.1	Mono	Eos	Herba Sec
9	4 F 181 183 184 186 187 197 197 198 200	16.9 18.4 16.9 17.0 17.0 17.0 16.7 16.7 16.3	8.2 8.7 8.7 8.8 8.2 8.2 8.2	47 48 48 47 50 50 48 49 46	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	57 58 58 78 78 60 60 88	36 38 36 37 44 44 44 44 45 44 45 45 45 45 45 45 45	1.2 1.2 1.2 1.0 1.0 1.4 1.0	7.4.0 2.2.2 2.2.2 2.3.8 4.6.2 7.8	0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0	8.4.00 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0.0000.2000.0000.0000.0000.0000.0000.0000.0000.0000	000000000000000000000000000000000000000	22.7 2.12 2.12 2.12 2.12 2.22 2.22 2.22
	Mean S.D.	16.8	8.4	48	07 1	57	35	1.2	5.2	0.7	1.4	0.1	0.0	21.9
250	5 F 202 203 205 209 212 212 212 213 214 214	15.7 15.9 17.9 16.7 16.8 16.9	7.6 7.8 8.5 8.4 8.1 8.0 9.0	48 49 50 47 49 49 49	21 57 57 57 57 57 57 57 57 57 57 57 57 57	63 59 59 60 60 60 60 74	E 5 8 5 4 4 4 4	1.2 0.8 0.8 1.2 1.9 0.6	6.2 6.2 7.8 6.3 1.9	1.3 0.8 0.5 0.7 0.6 1.0		0.1 0.1 0.1 0.1 0.0	0.1 0.1 0.0 0.0 0.0 0.1	23.5 22.2 22.2 21.2 21.3 21.3 7.22 7.22
750	Mean S.D. 6 F 223 225 239	16.5 0.7 16.5 15.1 16.8	8.2 0.5 9.0 7.4 8.6	49 1 49 47 50	70 70 70 70 70 70 70 70	60 87 87 88	35 37 37 38	1.1 0.4 1.2 1.0	5.6 6.5 9.5	0.8 0.3 0.6 0.6	5.8 5.8 8.6	0.1	0.0	22.0 0.8 0.8 21.7 21.2 21.2
	Mean S.D.	16.1	8.3	49	19	95 2	33	1.2	7.5	0.9	6.6	0.0	0.0	21.4

For remaining units see Appendix 15

APPENDIX 5

HMX: 13 Week Toxicity Study in Mice

Clinical Chemistry: Males Individual Values

 Dose
 Tests
 BUN
 Glu
 AST
 ALT
 AP
 LDH
 Na
 K
 TP
 Alb
 AG-R

 mg/kg
 Units
 mmol/mmol/mmol/mmol/mmol/glu
 10/1
 IU/1
 IU/1
 IU/1
 mmol/mmol/glu
 g/1
 g/1

 /day
 dcp S Arm
 1
 1
 1
 1
 1

30n 1 M 1 9.3 10.60 64 23 208 478 155 7.5 54 31 1.3 4 12.9 12.01 64 27 214 642 158 12.7 - 34 11.5 5 12.9 12.04 55 16 247 353 172 9.9 55 33 1.5 5 1.8 12.8 5.47 - 36 125 1459 173 10.4 57 33 1.5 1.6 10.4 4.08 69 - 20 208 871 171 13.3 57 34 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5		Grp S	Arm											
3 9.2 21.11 64 27 214 642 158 12.7 - 34 4 12.9 12.04 55 36 247 353 172 9.9 55 33 7 # 12.8 5.47 - 36 125 1459 173 10.4 57 33 110 \$ 11.8 4.96 55 32 - 43 166 15.7 55 33 111 10.4 4.08 69 - 208 871 171 13.3 57 34 15 78 27 234 916 78 27 234 916 78 27 234 916 78 27 234 916 78 27 234 916 78 27 234 916 78 27 234 916	G J	Ξ.	-	٠.٠	10.60	64	23	208	478	155	7.5	54	<u></u>	-
4 12.9 12.04 55 16 247 151 172 9.9 55 31 7 # 12.8 5.47 - 5 18 178 607 162 10.3 51 31 10 \$ 11.8 4.96 55 18 178 607 162 10.3 51 31 11			~	9.5	21.11	64	27	714	642	158	17.1	•	34	
5 9.1 14.50 55 18 178 607 162 10.3 51 31 10 \$1.2.8 5.47 - 36 125 1459 173 10.4 57 33 10 \$1.1.8 4.96 55 32 - 408 187 171 13.3 57 33 11 10.6 13.88 46 23 191 308 163 9.6 53 33 20 9.0 15.94 46 27 194 413 164 9.8 56 34 30 9.0 15.94 46 27 194 413 164 9.8 56 34 30 9.0 15.94 46 27 194 413 164 9.8 56 34 3.D 11 6 27 194 413 164 9.8 56 34 4 Mean 11 6 27 204 453 164 18 55 31 5			4	12.9	12.04	55	99	247	353	172	6.6	55	?	1.5
7 # 12.8 5.47 - 36 125 1459 173 10.4 57 33 11 10.4 4.08 69 - 208 871 171 13.3 57 34 15 17 10.6 13.8 46 27 214 916 15.7 55 33 34 20 9.0 15.94 46 27 194 413 164 9.8 56 34 20 9.0 15.94 46 27 194 413 164 9.8 56 34 25.D. 1.6 5.70 11 6 35 35 46 2.5 2 1 1 6.7 10.6 4.39 64 27 204 453 163 11.5 53 32 69 9.8 8.97 46 27 204 453 163 11.5 53 32 69 9.8 8.97 46 27 204 453 163 11.5 53 32 69 9.8 8.97 46 27 294 453 165 11.8 52 11 72 12.3 5.26 41 18 185 248 165 11.8 52 31 74 7.3 9.89 50 27 204 413 161 10.3 51 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 74 71 9.1 144 59 22 121 562 164 10.5 55 31 77 9.1 14.71 46 23 228 278 164 9.4 55 31 77 9.1 14.72 46 18 218 368 164 9.4 55 31			2	9.1	14.50	55	18	178	607	162	10, 3	51	31	1,6
10 \$ 11.8 4.96 55 32 - 403 166 15.7 55 33			7	17.8	5.47	1	36	125	1459	173	10.4	Ls,	33	1.4
11 10.4 4.08 69 - 208 871 171 13.3 57 34 15 - 78 27 234 916 - 7 - 78 27 234 145 - 7 - 7 19.6 13.8 46 23 191 308 163 9.6 53 33 34 15.0 15.94 46 27 194 413 164 9.8 56 34 12.0 16.6 11.34 59 28 200 645 165 11.0 55 31 11.6 5.70 11 6 35 354 6 2.5 2 1 1.6 5.70 11 6 35 32 45 11.6 5.30 45 163 11.5 53 32 48 12.6 5.33 44 27 204 453 164 10.5 53 32 46 27 128 164 10.8 54 32 46 27 128 164 10.8 54 35 31 47 128 5.26 41 18 185 248 165 11.8 52 31 47 11.44 59 22 124 473 31 47 46 23 228 278 164 10.5 55 33 47 46 23 228 278 164 10.5 55 33 47 46 23 228 278 164 10.5 55 33 47 46 23 228 278 164 9.4 55 33 33 47 46 23 228 278 164 9.4 55 33 33 47 46 23 228 278 164 9.4 55 33 33 34 34 36 36 36 36			10 \$	11.8	4.96	55	32	ı	403	166	15.7	55	33	1.5
15			=	10.4	4.08	69	ı	208	178	171	13,3	57	34	1.5
17 10.6 13.38 46 23 191 308 163 9.6 53 33 20 9.0 15.94 46 27 194 413 164 9.8 56 34 S.D. 1.6 11.34 59 28 200 645 165 11.0 55 33 S.D. 1.6 5.70 11 6 35 354 6 2.5 2 1 4 M 63 9.9 13.81 50 27 204 453 163 11.5 53 32 64 10.6 4.39 64 27 204 473 164 11.5 53 32 64 9.8 8.97 46 27 204 475 164 9.8 54 32 64 9.8 8.97 46 27 204 475 164 10.6 55 31 72 12.3 5.26 41 18 185 248 165 11.8 52 31 74 7.3 9.89 50 27 214 433 161 10.3 51 31 75 11.2 11.44 59 23 191 562 164 10.5 55 33 77 9.1 14.72 46 18 218 308 164 9.4 55 33 79 8.4 14.72 46 18 218 308 164 9.4 55 33 70 9.1 14.71 46 23 228 278 164 55 33 70 9.1 14.72 46 18 218 308 164 9.4 55 33 70 9.1 14.72 46 18 218 308 164 9.4 55 33 70 9.1 14.72 46 18 218 308 164 9.4 55 33 71 72 73 73 73 73 73 73 73			15	ŀ	,	78	27	234	916	,	•	•	,	
Mean 10.6 11.34 59 28 200 645 165 11.0 55 33 S.D. 1.6 5.70 11 6 35 354 6 2.5 2 1 A M 63 9.9 13.81 50 27 204 453 163 11.5 53 32 68 12.6 5.33 41 18 201 388 162 13.6 55 32 72 12.3 5.26 41 18 185 248 165 11.8 52 31 74 7.3 9.89 50 27 214 413 161 10.3 51 75 11.2 11.44 59 23 121 562 164 10.5 55 32 76 81 15.58 59 21 111 562 13.6 55 31 77 9.1 14.71 46 23 228 278 160 9.5 55 33 79 8.4 14.72 46 18 18 50 64 10.5 55 33			11	10.6	13.38	46	73	161	308	163	9.6	53	33	1.7
Mean 10.6 II.34 59 28 200 645 165 11.0 55 33 S.D. 1.6 5.70 11 6 35 354 6 2.5 2 1 A M 63 9.9 I.3 BI 50 27 204 453 163 11.5 53 32 69 1.0.6 4.39 64 27 204 712 164 9.8 54 32 69 9.8 8.97 46 27 214 418 165 11.6 55 31 72 12.3 5.26 41 18 185 248 165 11.8 52 31 74 7.3 9.89 50 27 214 413 161 10.5 55 32 75 11.2 11.4 45 27 114 413 161 10.5 55 31 77 9.1 14.7			50	9.0	15.94	46	17	194	413	164	9.8	95	34	1.5
S.D. 1.6 5.70 11 6 35 354 6 2.5 2 1 4 M 63 9.9 13.81 50 27 204 453 11.5 53 32 68 12.6 5.33 44 27 198 776 164 9.8 54 32 69 9.8 8.97 46 27 198 776 169 9.8 58 35 72 12.3 5.26 41 18 185 248 165 11.8 52 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 76 81.15.58 59 23 129 578 119 56 33 77 9.114.71 46 23 228 278 164 9.4 55 33 79 8.4 14.7.7 46 18 218 308 46 9.4 55 33		Mean		10.6	11.34	59	82	200	645	165	11.0	55	=	1.5
4 M 63 9.9 13.81 50 27 204 453 163 11.5 53 32 68 12.6 5.33 41 18 20 12 164 9.8 54 32 69 9.8 8.97 46 27 198 776 169 9.8 58 35 72 12.3 5.26 41 18 185 248 165 11.8 52 31 74 7.3 9.89 50 27 214 413 161 10.3 51 31 76 81.115.58 59 23 121 56 164 10.5 55 32 77 9.1 14.7.1 46 23 228 278 164 9.4 55 33 79 8.4 14.7.2 46 18 218 368 164 9.4 55 33		S.D.		1.6	5,70	=	9	35	354	9	5.5	7	-	0.1
10.6 4.39 64 27 204 712 164 9.8 54 32 12.6 5.33 41 18 201 388 162 13.6 55 32 9.8 8.97 46 27 198 776 169 9.8 58 35 12.3 5.26 41 18 185 248 165 11.8 52 31 7.3 9.89 50 27 214 413 161 10.3 51 31 11.2 11.4 59 23 121 478 - - - - 31 9.1 14.71 46 23 228 278 160 9.5 55 33 8.4 14.72 46 18 218 368 164 9.4 55 33	0£	Σ.	63	9.6	13.81	50	7.7	204	453	[63	11.5	53	32	1.5
12.6 5, 33 41 18 201 388 162 13.6 55 32 9,8 8, 97 46 27 198 776 169 9, 8 58 35 12,3 5,26 41 18 185 248 165 11, 8 52 31 7,3 9,89 50 27 214 413 161 10,3 51 31 11,2 11,44 59 23 171 478 - - - 31 9,1 14,71 46 23 228 278 160 9,5 55 33 8,4 14,72 46 18 218 368 164 9,4 55 33			41	10.6	4. 39	54	77	204	711.5	164	8.6	54	32	1:5
9.8 8.97 46 27 198 776 169 9.8 58 35 12.3 5.26 41 18 185 248 165 11.8 52 31 7.3 9.89 50 27 214 413 161 10.3 51 31 11.1 59 23 171 46 10.5 55 32 8.1 15.58 59 32 171 478 - - - 31 9.1 14.71 46 23 228 278 160 9.5 55 33 8.4 14.72 46 18 218 368 164 9.4 55 33			89	17.6	5, 33	41	18	707	388	162	13.6	55	32	1.4
12.3 5, 26 41 18 185 248 165 11.8 52 31 7.3 9,89 50 27 214 413 161 10.3 51 31 11.2 11.44 59 23 191 56 164 10.5 55 32 8.1 15,78 59 32 171 478 - - - 31 9.1 14,72 46 18 218 368 164 9,4 55 33			69	9.6	8.97	46	23	861	176	691	9.6	28	35	:
7,3 9,89 50 27 214 413 161 10,3 51 31 11,2 11,44 59 23 191 562 164 10,5 55 32 8,11 5,58 59 32 171 478 31 9,1 14,71 46 23 228 278 160 9,5 55 33 8,4 14,72 46 18 218 368 164 9,4 55 33			7.5	12.3	2.26	41	18	185	248	165	11.8	25	31	:
11.2 11.44 59 23 191 562 164 10.5 55 32 8.1 15.58 59 32 171 478 31 9.1 14.71 46 23 228 278 160 9.5 55 33 8.4 14.72 46 18 218 368 164 9.4 55 33			74	7.3	9.89	ß	1.7	214	4 ! 3	191	10.3	75	₹	1.6
8.1 15.58 59 32 171 478 31 9.1 14.71 46 23 228 278 160 9.5 55 33 8.4 14.72 46 18 218 368 164 9.4 55 33			75	11.2	11.44	59	53	191	295	164	10.5	55	32	l.4
9.1 14.71 46 23 228 278 160 9.5 55 33 8.4 14.72 46 18 218 368 164 9.4 55 33			9/	8.1	15,58	65	??	171	478	,	1	,	3	
8.4 14.72 46 18 218 368 164 9.4 55 33			11	9.1	14.71	46	23	228	278	160	9.5	55	33	1:5
			79	8.4	14.72	46	18	218	368	164	9.4	55	33	1.5

* Arm 7 AST Value of 15110/1 Omitted from Mean \$ Arm 10 AP Value of 51510/1 Omitted from Mean

1.5 1.5 1.5 0.1

> 164 10.7 3 1.4

> 470

201 17

24

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9.9 10.41 1.8 4.32

Mean S.D.

APPENDIX 5 (continued)

25	OULTS	1 CIE	1 (1)	1071	10/1	10/1	10/1	mmol/ 1	/lownrian	9/1	9/1	
75	irp S Anm	ı						ı				
	5 M 81	6.9	11.65	~~	23	217	672	163	8.2	54	=	1.
	82	6,3	15.52	S.	73	707	448	157	4°F	48	53	7:
	84	6.7	18.27	64	81	234	353	154	9.5	49	53	1.5
	85	8.6	4.40	7	23	127	976	158	12.3	25	8	1.4
	87	7.9	8.00	13	27	194	1095	191	11.2	48	28	7:
	83	8.6	9.75	ı	53	221	418	191	10.4	53	=	1.4
	16	111.2	6.64	,	35	717	976	160	14.1	99	32	=
	92	9.4	7.12	41	23	184	398	159	15.4	20	53	1.4
	93	6.9	14.06	73	41	111	196	159	11.1	51	53	-
	46	7.4	13,75	9	£	194	343	160	10.7	48	53	1.5
	Mean		10.92]]	27	197	638	159	11.2	51	2	1.4
	S.D.	1.5	4.46	20	7	30	281	2	2.2	~	-	0.1
200	6 ₩ 101	8,3		64	18	214	517	170	11.1		32	[
		9.0		22	53	85	1419	175	13.0	,	33	
	105	8.7		20	18	211	672	184	11.5	63	34	
	109	7.3		5	RΤ	214	1 384	172	13.7	19	33	1.2
	110	7.1	2,78	18	18	184	672	146	7.5	54	8	1:3
	112	8.1		64	7.7	174	71.2	158	13.5	48	27	-
	Mean	8.1	7.39	55	82	180	968	168	11.7	56	32	1.2
	S.D.	0.8	3.98	50	4	20	397	13	2.3	9	٣	0.1

- Insufficient Sample # Arm 91 AST Value of 138 IU/1 Omitted from Mean

APPENDIX 6

HMX: 13 Week Toxicity Study in Mice

Clinical Chemistry: Females

Individual Values

				•	7 4 7 7	•						
Dose mg/kg /day	Tests Units Grp S Anm	BUN mmol/ 1	Glu marol/	AST IU/1	ALT IU/1	AP 1U/1	LDH 10/1	Na mmol/ l	K mmol/ 1	тР 9/1	Alb g/l	AG-R
OO	1 F 121 124 125 127 137 133 134 136 137 139	13.7 10.5 9.4 9.5 12.1 8.4 12.8	15.43 19.54 7.23 5.78 3.88 17.21	46 27 44 46 46 47 47 47 47 47 47 47 47 47 47 47 47 47	32 32 32 113 118 118 18 18 18	294 435 391 341 318 251 341 314	811 522 428 388 527 527 756 1045	164	11:1	55 55 60 63 88	, 25, 28, 28, 28, 28, 28, 28, 28, 28, 28, 28	1.3
	Mean S.D.	10.5	12.50 5.99	62	21	337 53	628 231	158 8	10.0	60	34	1.4
30	3 F 161 162 165 169 170 171 171 178 178	12.0 13.7 13.9 13.9 13.2 13.7 10.2	26.33 19.24 3.82 7.44 6.05 10.85 13.66	18 78 82 82 82 46 59 50 50 59	23 23 23 23 23 23 23	288 257 284 328 328 304 308 365 341	1817 1005 617 707 463 458 542 313 796	- - - 187 163 163	- - - - 17.4 10.3 10.5	65 - 68 65 - 68 65 - 68 65 - 68	25 - 45 - 45 - 45 - 45 - 45 - 45 - 45 -	1.2
	Mean S.D.	12.7	12.65	58 21	28 12	307	746	170	12.1 3.5	63	36	1.3

- Insufficient Sample

APPENDIX 6 (continued)

4 06	Units 3rp S Anm	Impol/	1 mmol/	10/1	10/1	1/21	10/1	immo L/	mmol/ 1	9/1	9/1	:]
	4 F 181 183 184 186 187 193 196 197 198	8.7 9.7 10.2 13.1 9.5 9.5 8.8 8.8	17.16 16.17 17.36 13.48 13.48 13.48 7.13 9.78 12.42 11.46	105 53 54 54 46 105 46	23 23 23 23 23 23 23	288 335 378 351 284 348 335 311	1020 443 443 458 502 637 647 1449 607 966	159 168 167 168 164 161	9.2 10.8 10.2 10.6 10.0 - 8.6 - 13.1	60 60 60 63 63 63	36 4 8 8 9 8 9 8 9 8 9 8 9 8 9 8 9 8	
Me S.	Mean S.D.	4.4	12.62	99	£,	67 <u>7</u>	763	167	10.4	19 1	35 1	1.4
250 5	5 F 202 203 205 209 212 212 214 214	8.1 12.0 11.2 8.3 10.7 7.7	18.69 9.41 13.82 19.26 14.38 5.18	22×32×3	23 % E E E E E E E E E E E E E E E E E E	274 321 291 291 231 247 244	1000 981 946 333 612 557	167	1,11,8,1	2.00 E 2.00 C C C C C C C C C C C C C C C C C C	######################################	- 75.1
S.	Mean S.D.	10.0	13.45 4.45	88 21	2 *	277	787	197	В.7	£~	~ -	0.1

APPENDIX 7

HMX: 13 Week Toxicity Study in Mice Urinalysis: Individual Values - Males

Dose mg/kg/day	1.D.	Hd	SG	Vol	Prot-	Glucose	Glucose Ketones	B111-	Urobil	Blood p19-	Colour			MICR	MICROSCOPY	PY		
mg/kg/day	/sex	•		T W	eın			rubin	ınogen	ments		3	CR	м	æ	0	Ü	<
Control	13		1.007	a<0.5							ĀЬ	0	0	0	0	0	-	0
*	3																	•
*	4																	
	S	8.0	1.036	0.5	-	0	0	0	<u> </u>	-	GRY	0		0	0		0	0
*	7																	
	10	8.0	1.042	1.0	1	0	0	0	0	0	ΓX	0	-	0	0	7	0	0
*	11																	
*	15																	
*	17															_		
	20		1.048	a<0.5							λd	0	_	0	0	0	0	0
	Mean	8.0	1.033	0.8														
	s.D.	0.0	0.018	4.0														
30 *	۶٤9																	
•	29																	
*	89																	
*	69																	
	72		1.041	<0.5							GRY	0	_	•	•	_		•
•	74																	
*	75														-			
	9/		1.015	<0.5							ΡΥ	1	-	0	0	-	_	•
•	11							-										
•	79										_							
	Mean		1.028															
	s.D.		0.018															
														1	1	1	1	7

* = No sample obtained

a = Value omitted from mean

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O 000000000 000000 -----7 - 1 - 1 - 7 MICROSCOPY 0 CR -----. 0 0 0 0 0 0 Colour ру Ру Ру Ру Ру Blood pig-ments 0 0 0 0 0 0 0 0 0 0 0 0 0 0 Urobil inogen 0 0 0 0 0 0 0 0 0 0 0 0 0 0 Bill-rubin 0 0 0 0 0 0 0 0 0 0 0 0 Ketones 000000000 0 0 0 0 0 Glucose 000000 0 0 0 0 0 0 0 0 Prot-ein 0 0 0 0 0 0.5 <0.5 0.5 0.7 0.3 0.5 0.5 0.6 Vol 1.036 1.019 1.019 1.015 1.016 1.016 1.013 1.015 1.018 0.007 1.016 1.023 1.014 1.010 1.013 1.014 1.010 1.020 1.011 1.009 SG 9.0 9.0 7.0 8.1 6.0 6.5 7.0 6.9 펎 I.D. /Sex Mean S.D. Mean 1013 S.D. 103 105 109 110 882 885 887 891 992 993 Dose mg/kg/day 200 75

APPENDIX 7 (continued)

a = Value omitted from mean

APPENDIX 8

HMX: 13 Week Toxicity Study in Mice Urinalysis: Individual Values - Females

Dose	I.D.	200	JS	Vol	Prot-	esoonto	Ketones	Bi11-	Urob11	Blood plg-	Colour			MICROSCOPY	osco	λď		
ıg/kg/day	/Sex	i.	3	Tw .	ein			rubin	Inogen	ments		3	CR	3	æ	0	c	4
Control	1219	8.0	1.016	1.0	7	0	0	0	0	2	ГУ	0	ī	0	0	7	0	0
	124	7.0	1.016	1.0	1	0	0	0	0	-	LY	0	7	0	0	0	7	0
	125	8.5	1.020	1.0	-	0	0	0	0	-	GRY	0	-	0	0	-	-	0
	127	9.0	1.017	1.0	-	0	0	0	0	0	LY	0	7	0	0	-	-	0
	132	8.0	1.016	0.5	_	,	0	0	0	3	GRY	0	7	0	0	7	0	0
	133	0.6	1.018	1.0	-	0	0	0	0	0	LY	0	_	•	0	-	-	•
	134	7.5	1.023	1.5	-	0	0	0	0	0	LY	0	-	0	0		0	•
	136	8.0	1.024	1.0	-	0	0	0	0	0	LY	0	-	•	0	0	0	0
	137	7.0	1.016	0.5	-	2	0	0	0	2	GRY	0	2	0	0	2	0	0
	139	8.0	1.013	0.5	1	0	0	0	0	0	Γλ	0	0	0	0	-	0	0
	Mean	8.0	1.018	6.0														
	S.D.	0.7	0.003	0.3														
30	1619	8.0	1.020	0.5	1	1	0	0	0	0	LY	0	-	0	0	-	0	0
	162	8.0	1.020	1.0	-	1	0	0	0	0	LY	0	1	•	0	2	0	•
	165	8.0	1.014	0.5	-	0	0	0	0	0	LY	0	-	0	0	-	0	0
	166	9.0	1.016	1.0	~	~	0	0	0	~	GRY	0	2	0	0	~	0	0
	169	8.0	1.018	1.0	-	0	0	0	0	0	Ľ	0	2	0	0	-	0	0
	170	8.0	1.024	1.0	7	-	0	0	0		GRY	0	7	0	0	С	0	0
	172	8.5	1.018	1.0	-	0	0	0	0	0	LY	0	7	c	0	-	0	•
	176	0.6	1.015	1.0			0	0	0	-	GRY	0	-	0	0	7	0	0
	178	9.0	1.018	1.0	-	-	0	0	0	-	LY	0	2	0	0	-	0	•
	179	8.0	1.012	0.5	-	0	0	0	0	0	LY	0	-	0	0	-	0	0
	Mean	8.4	1.018	6.0														
	s.D.	0.5	0.003	0.2														

0 1 0 - 3 - 1 - 1 - 1 MICROSCOPY 00000000 0 0 0 0 0 0 3 000000000 00000000 CR 0 0 0 0 0 0 0 0 0 00000000 Colour PY LY LY GRY GRY LY GRY LY
LY
GRY
LY
LY
LY
LY
LY
CRY
GRY
GRY LY Blood pig-ments 0 0 0 0 Urobil inogen 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 Bill-rubin 000000000 0 0 0 0 0 0 0 Ketones 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 Glucose - 0 0 0 0 0 0 Prot ein 0.3 1.0 Vol ml 1.015 1.015 1.015 1.015 1.016 1.022 1.012 1.023 1.019 1.020 1.019 1.018 0.003 1.015 1.018 1.016 1.044 1.021 1.026 1.019 1.031 1.023 0.009 SG 8.0 8.5 8.0 8.0 8.0 9.0 6.5 7.0 8.5 8.0 8.0 9.0 8.0 8.0 8.4 描 Mean S.D. Mean S.D. 1819 183 2029 I.D. 193 203 205 198 184 186 187 197 200 Dose mg/kg/day 250 90

APP: :DIX 8 (continued)

APPENDIX 9

HMX: 13 Week Toxicity Stuay in Mice Absolute Organ Weight (g) Individual Values - Premature Decedents (Males)

es R	61.0	NW 0.16	91.0	0.14	0.13	0.11	M	N.	M Z	0.17	0.14	0.09	0.18	A Z
Testes	0.16	NW 0.15	0.16	0.14	0.13	0.11	MN	MN	MN	0.17	0.15	0.11	0.16	M.
Spleen	0.04	0.04	0.05	0.04	0.05	0.05	0.04	90.0	90.0	90.0	0.07	0.50	0.07	90.0
Lungs	0.19	0.18	0.25	0.17	0.21	3N	0.32	0.21	0.19	0.23	0.26	MN	0.23	0.20
Liver	1.47	1.26	1.61	1.41	1.46	1.27	1.73	1.72	1.70	1.69	1.41	1.05	1.72	1.58
eys R	0.33	0.24	0.24	0.23	0.26	0.22	0.23	0.26	0.27	0.29	0.27	0.19	0.28	0.33
Kidneys L	0.30	0.21	0.23	0.21	0.23	0.21	0.22	0.23	0.27	0.28	0.29	0.18	0.26	0.29
Heart	0.15	0.18	0.15	0.14	0.16	0.16	0.18	0.16	0.21	0.20	0.20	0.14	0.18	0.15
Brain	0.46	0.41	0.45	0.45	0.49	0.43	0.47	0.48	0.49	0.52	0.46	0.45	0.49	3 Z
Body Weight (9)	7.2	21 26	21	21	23	20	24	25	27	56	24	17	27	24
Week of Death	14	4	2	r 2	7	2	9	4	S	6	2	1	9	80
Animal Number	18	88 94	102	104	107	108	111	113	115	116	117	118	119	120
Dose Level/ (mq/kq/day)	305	75&	2003											

Nw = not weighed

APPENDIX 10

HMX: 13 Week Toxicity Study in Mice Absolute Organ Weights (q) Individual Values - Premature Decedents (Females)

	Spleen	0.04	0.10	90.0	0.07	0.07	90.0	90.0	0.07	0.08	0.08	0.07	90.0	0.07	90.0	90.0	0.07	0.10	0.07
	Lungs	0.16	91.0	0:0	0.32	0.26	0.16	0.21	0.23	0.19	0.20	0.22	0.21	0.21	0.30	MN	0.23	0.27	0.21
!	Liver	0.70	1.63	1.99	1.56	1.51	1.48	1.74	1.78	1.41	1.41	1.82	1.69	2.18	1.85	1.34	1.87	1.88	1.61
	eys R	0.16	0.20	0.20	0.21	0.17	0.18	0.20	0.21	0.15	0.19	0.19	0.22	0.21	0.21	0.17	0.19	0.21	0.19
	Kidneys L	0.15	0.20	0.19	0.22	0.18	0.17	0.18	0.22	0.16	0.17	0.19	0.20	0.20	0.25	0.17	0.12	0.19	0.19
i	Heart	0.13	0.16	0.17	0.17	0.16	0.15	0.17	0.15	0.13	0.15	0.15	0.17	0.17	0.18	0.15	0.17	0.15	0.15
	Brain	0.45	0.43	0.50	0.44	0.47	0.45	0.47	0.50	MN	0.47	0.48	0.44	3 N	0.54	n.46	0.49	0.50	0.48
	Week of Deaths	11	9	10	12	01	4	6	10	т	80	10	10	6	11	2	7	13	٣
	Body Weight (q)	19	22	27	25	24	21	23	27	18	23*	25	25	56 *	29	19	25	25	23
	Animal Number	131	168	201	204	206	207	208	210	211	215	216	217	218	219	221	222	223	224
	Group/Sex Dose Level	∂0	304	250%												7507			

* = Animal room body weight

NW = not weighed

APPENDIX 10 (continued)

750Y 225 28 13 0.51 0.19 0.22 0.15 0.19 0.15 0.15 0.19 0.15 0.16 0.15 0.19 0.15 0.16 0.15 0.19 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.16 0.17 0.16 0.16 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.16 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.16 0.15 0.16 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15 0.15	Group/Sex Dose Level	Animal Number	Body Weight (g)	Week of Deaths	Brain	Heart	Kidneys L	eys R	Liver	Lungs	Spleen
20 1 0.45 0.15 0.16 0.15 1.57 NW 19 2 0.47 0.13 0.15 1.44 NW 25 10 0.47 0.13 0.15 1.44 NW 19 2 0.47 0.12 0.20 1.81 0.28 19 3 0.47 0.11 0.14 0.15 1.16 0.25 24 9 0.46 0.18 0.18 0.17 1.21 0.16 19 2 0.46 0.18 0.18 0.17 1.44 NW 18 2 0.46 0.16 0.18 0.17 1.44 NW 23 0.45 0.16 0.18 0.15 1.21 0.16 24 9 0.45 0.16 0.19 0.15 0.15 0.15 23 1 0.49 0.16 0.19 0.19 0.19 0.19 24 1	4057	225	28	13	0.51	0.19	0.22	0.23	2.16	0.39	0.13
19 2 0.47 0.13 0.15 0.16 1.44 NW 25 10 0.51 0.20 0.20 1.81 0.28 19 2 0.47 0.12 0.16 0.16 0.16 0.15 19 3 0.47 0.11 0.14 0.15 1.55 0.25 18 3 0.47 0.11 0.14 0.15 1.55 0.25 19 0.46 0.18 0.16 0.18 0.18 0.16 0.18 0.16 0.18 0.18 0.16 0.18 0.16 0.18 0.15 0.15 0.15 19 0.46 0.16 0.19 0.17 1.44 NW 18 0.45 0.16 0.19 0.15 0.15 0.15 0.15 24 9 0.49 0.16 0.19 0.19 0.19 0.19 0.19 22 7 0.49 0.11 0.19 0.19		526	20	7	0.45	0.15	0.16	0.15	1.57	MN	0.05
25 10 0.51 0.20 0.20 1.81 0.28 19 2 0.47 0.12 0.16 0.16 1.16 0.25 19 3 0.47 0.11 0.16 0.16 1.16 0.25 18 3 0.47 0.11 0.16 0.15 1.55 0.25 24 9 0.46 0.18 0.18 0.17 1.44 NW 18 2 0.46 0.16 0.18 0.17 1.44 NW 18 2 0.46 0.16 0.18 0.17 1.44 NW 23 8 0.49 0.16 0.19 1.33 0.15 24 9 0.49 0.16 0.19 1.34 0.24 23 3 0.46 0.17 0.19 0.19 0.19 0.19 24 13 0.49 0.13 0.16 0.17 0.19 0.11 24<		227	19	2	0.47	0.13	0.15	0.16	1.44	MN	90.0
19 2 0.47 0.12 0.16 0.16 1.16 0.25 19 3 0.47 0.11 0.14 0.15 1.15 0.25 18 3 0.47 0.11 0.14 0.15 1.55 0.25 24 9 0.46 0.18 0.18 0.17 1.44 NW 19 2 0.46 0.16 0.18 0.17 1.44 NW 18 2 0.46 0.16 0.19 0.17 1.44 NW 23 8 0.49 0.16 0.19 0.21 1.79 0.15 24 9 0.49 0.16 0.19 0.19 1.34 0.29 25 7 0.49 0.17 0.19 0.19 0.19 0.17 24 13 0.46 0.17 0.19 0.17 1.49 0.17 24 13 0.47 0.17 0.14 0.11		228	25	10	0.51	0.21	0.20	0.22	1.81	0.28	0.54
19 3 0.47 0.11 0.14 0.15 1.55 0.25 18 3 0.47 0.14 0.16 0.17 1.21 0.16 24 9 0.46 0.18 0.18 1.77 0.32 19 2 0.46 0.16 0.18 0.17 1.44 NW 18 2 0.46 0.16 0.19 0.15 1.33 0.15 23 8 0.49 0.16 0.19 0.21 1.79 0.21 24 9 0.49 0.18 0.21 0.19 1.34 0.24 25 7 0.49 0.17 0.19 1.34 0.29 27 7 0.49 0.13 0.16 0.17 1.49 0.17 24 13 0.47 0.17 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		229	19	2	0.47	0.12	0.16	0.16	1.16	0.25	0.07
18 3 0.47 0.14 0.16 0.17 1.21 0.16 24 9 0.46 0.18 0.18 0.19 1.77 0.32 19 2 0.46 0.16 0.18 0.17 1.44 NW 18 2 0.45 0.11 0.14 0.15 1.33 0.15 23 8 0.49 0.16 0.19 0.21 1.79 0.21 24 9 0.49 0.18 0.21 0.19 1.97 0.24 23 3 0.46 0.17 0.19 0.19 0.19 0.21 24 13 0.46 0.17 0.19 0.17 1.49 0.17 24 13 0.49 0.11 0.16 0.17 1.49 0.17 24 13 0.49 0.11 0.16 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14		230	19	٣	0.47	0.11	0.14	0.15	1.55	0.25	0.05
24 9 0.46 0.18 0.18 0.18 1.77 0.32 19 2 0.46 0.16 0.18 0.17 1.44 NW 18 2 0.45 0.11 0.14 0.15 1.33 0.15 23 8 0.49 0.16 0.19 0.21 1.79 0.21 24 9 0.49 0.18 0.21 0.19 1.97 0.24 23 3 0.46 0.17 0.19 0.19 1.34 0.29 24 13 0.49 0.13 0.16 0.17 1.49 0.17 24 13 0.49 0.13 0.16 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		231	18	~	0.47	0.14	0.16	0.17	1.21	0.16	90.0
19 2 0.46 0.16 0.18 0.17 1.44 NW 18 2 0.45 0.11 0.14 0.15 1.33 0.15 23 8 0.49 0.16 0.19 0.21 1.79 0.15 24 9 0.49 0.18 0.21 0.19 1.34 0.24 23 3 0.46 0.17 0.19 0.19 1.34 0.29 24 13 0.49 0.13 0.16 0.17 1.49 0.17 14 1 0.46 0.11 0.12 0.14 0.83 NW		232	24	6	0.46	0.18	0.18	0.18	1.77	0.32	0.07
18 2 0.45 0.11 0.14 0.15 1.33 0.15 23 8 0.49 0.16 0.19 0.21 1.79 0.21 24 9 0.49 0.18 0.21 1.79 0.21 23 3 0.46 0.17 0.19 1.34 0.24 22 7 0.49 0.13 0.16 0.17 1.49 0.17 24 13 0.47 0.17 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		233	61	2	0.46	0.16	0.18	0.17	1.44	MN	0.05
23 8 0.49 0.16 0.19 0.21 1.79 0.21 24 9 0.49 0.18 0.21 0.19 1.97 0.24 23 3 0.46 0.17 0.19 1.34 0.29 22 7 0.49 0.13 0.16 0.17 1.49 0.17 24 13 0.47 0.17 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		234	18	2	0.45	0.11	0.14	0.15	1.33	0.15	0.05
24 9 0.49 0.18 0.21 0.19 1.97 0.24 23 3 0.46 0.17 0.19 0.19 1.34 0.29 22 7 0.49 0.13 0.16 0.17 1.49 0.17 24 13 0.47 0.17 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		235	23	œ	0.49	0.16	0.19	0.21	1.79	0.21	0.07
23 3 0.46 0.17 0.19 0.19 1.34 0.29 22 7 0.49 0.13 0.16 0.17 1.49 0.17 24 13 0.47 0.17 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		236	24	6	0.49	0.18	0.21	0.19	1.97	0.24	90.0
22 7 0.49 0.13 0.16 0.17 1.49 0.17 24 13 0.47 0.17 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		237	23	~	0.46	0.17	0.19	0.19	1.34	0.29	90.0
24 13 0.47 0.17 0.24 0.23 1.57 0.31 14 1 0.46 0.11 0.12 0.14 0.83 NW		238	22	7	0.49	0.13	0.16	0.17	1.49	0.17	0.07
14 1 0.46 0.11 0.12 0.14 0.83 NW		239	24	13	0.47	0.17	0.24	0.23	1.57	0.31	0.11
		240	14	-	0.46	0.11	0.12	0.14	0.83	MN	MN

NW = not weighed

APPENDIX 11

HMX: 13 Week Toxicity Study in Mice Absolute Organ Weights Individual Values - Terminal Sacrifice (Males)

Dose Level/Sex (mq/kq/day)	Animal Number	Body Weight (9)	Brain	Heart	K1dneys L R	leys R	Liver	Lungs	Spleen	Testes L	es R
0.3	7	25	0.45	0.15	0.27	0.28	1.45	0.16	90.0	0.18	0.19
	2	28	0.46	0.16	0.28	0.29	1.45	0.18	0.07	0.17	0.19
	~	26	0.43	0.15	0.25	0.27	1.27	0.18	0.07	0.21	0.20
	4	25	0.44	0.16	0.26	0.27	1.41	0.17	90.0	0.17	0.19
	5	27	0.45	0.16	0.27	0.27	1.20	0.15	0.07	0.16	0.17
	9	26	05.0	0.15	0.28	0.29	1.31	0.22	0.05	0.13	0.17
	7	26	0.45	0.17	0.28	0.31	1.48	0.16	0.07	0.18	0.19
	œ	27 ^D	0.46	0.18	0.27	0.30	1.43	0.16	90.0	0.15	0.18
	6	26	0.46	0.16	0.26	0.27	1.22	0.17	0.07	0.17	0.18
	10	24	0.46	0.14	0.24	0.26	1.13	0.17	0.07	0.19	0.18
	11	26	0.47	0.14	0.25	0.27	1.17	0.20	0.05	0.17	0.19
	1.2	27	0.45	0.17	0.27	0.30	1.38	0.18	0.07	0.19	a2.06
	13	26	0.42	0.14	0.26	0.28	1.36	0.17	0.05	0.17	0.15
	14	26	0.45	0.16	0.27	0.28	1.46	0.19	90.0	0.18	0.17
	15	25	0.41	0.14	0.28	0.28	1.16	0.17	0.08	0.17	0.17
	16	25	0.43	0.16	0.27	0.28	1.40	0.20	90.0	0.18	0.16
	17	26	0.45	0.15	0.25	0.27	1.17	0.15	90.0	0.18	0.18
	18	26	0.43	0.14	0.22	0.25	1.18	0.17	90.0	0.17	0.18
	61	28	0.47	0.16	0.26	0.29	1.34	0.18	0.07	0.16	0.18
	20	30	0.47	0.17	0.28	0.30	1.51	0.16	0.07	0.19	0.20
	M an	26.3	0.451	0.156	0.272	72	1.324	0.175	0.064	0.	0.177
	S.D.	1.3	0.020	0.012	0.017	17	0.126	0.018	0.008	0	0.015

a = omitted from mean due to suspected erroneous data b = Animal room weight

APPENDIX 11 (continued)

																	_				1		7
es R	0.19	0.19	0.19	0.17	0.17	0.19	0.16	0.14	0.18	0.18	0.19	0.19	0.18	0.18	0.17	0.18	0.17	0.19	0.19	0.18	0.177	0.014	
Testes I.	07.0	0.18	0.19	0.17	0.17	0.17	0.16	0.13	0.18	0.18	0.19	0.18	0.17	0.17	0.17	0.19	0.17	0.18	0.15	0.18	0.	•	
Spleen	6,03	0.06	0.06	0.06	0.06	90.0	90.0	90.0	90.0	0.08	0.07	80.0	0.07	0.07	0.05	0.07	90.0	0.07	0.07	90.0	0.065	0.008	
Lungs	0.20	07.0	0.19	0.21	0.19	0.20	0.18	0.16	0.14	0.23	0.19	0.19	0.14	0.18	0.13	0.18	0.15	0.17	0.17	0.18	0.179	0.025	
Liver	1.67	1.29	1.24	1.31	1.23	1.31	1.52	1.34	1.30	1.56	1.65	1.31	1.25	1.27	1.32	1.41	1.18	1.44	1.23	1.42	1.363	0.141	
leys R	0.32	0.26	0.28	0.24	0.27	0.28	0.32	0.27	0.26	0.32	0.30	0.31	0.28	0.30	0.24	0.31	0.25	0.31	0.28	0.30	0.278	0.029	
Kidneys L R	0.31	0.26	0.28	0.26	0.25	0.25	0.28	0.26	0.24	0.33	0.29	0.28	0.24	0.26	0.23	0.32	0.22	0.31	0.26	0.27	0.	0.	
Heart	0.17	0.14	0.14	0.15	0.15	0.14	0.16	0.15	0.14	0.17	0.15	0.16	0.16	0.15	0.13	0.18	0.14	0.18	0.14	0.15	0.153	0.014	
Brain	0.47	0.44	0.43	0.44	0.46	0.45	0.42	0.40	0.46	0.49	0.46	0.47	0.48	0.41	0.43	0.48	0.46	0.45	0.42	0.46	0.449	0,025	
Body Weight (9)	31	25	26	76	25	27	27	24	24	32	32	28	26	56	28	28	26	30	56	26	27.2	2.4	
Animal Number	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	336	37	38	39	40	Mean	S.D.	
Dose Level/Sex (my/kg/day)	54																		-				

0.17 0.16 0.21 0.18 0.19 0.18 0.17 0.17 0.19 0.18 0.17 0.18 0.17 0.18 0.16 0.17 0.21 œ 0.014 Testes L R 0.18 0.19 0.18 0.19 0.18 0.18 0.18 0.16 0.19 0.15 0.17 0.16 0.21 Spleen 0.061 0.011 0.02 90.0 0.07 90.0 90.0 90.0 0.07 90.0 0.07 0.05 0.07 0.07 90.0 90.0 90.0 90.0 0.07 90.0 0.030 0.186 Lungs 0.17 0.18 0.16 0.15 0.18 0.17 0.24 0.22 0.14 0.16 0.16 0.21 1.335 Liver 1.16 1.42 1.26 1.57 1.40 1.41 1.37 1.34 1.23 1.44 1.31 1.21 1.47 1.21 96.0 0.30 0.30 0.32 0.27 0.33 0.25 0.27 0.28 0.28 0.33 0.29 0.27 0.28 Kidneys L R 0.024 0.286 0.30 0.27 0.31 0.23 0.27 0.27 0.27 0.33 0.29 0.28 0.27 0.27 0.27 0.27 0.31 0.154 0.011 Heart 0.16 0.15 0.16 91.0 0.13 0.14 0.15 0.14 0.16 0.15 0.16 0.17 0.16 0.453 0.016 Brain 0.42 0.46 0.45 0.46 0.47 0.45 0.43 0.45 0.45 0.46 0.45 0.44 0.47 0.47 0.47 3 Body Weight (9) 27.4 26 27 28 28 25 31 Animal Number Mean S.D. 4 Level/Sex (mq/kq/day) 123 Dose

APPENDIX 11 (continued)

NW = not weighed

APPENDIX 11 (continued)

27 0.51 0.17 0.30 0.27 1.63 32 0.51 0.17 0.28 0.31 1.66 28 0.47 0.18 0.29 0.30 1.29 28 0.45 0.14 0.27 0.32 1.63 26 0.48 0.16 0.26 0.26 1.18 27 0.48 0.16 0.26 0.25 1.18 25 0.44 0.16 0.26 0.25 1.18 27 0.43 0.16 0.26 0.25 1.18 27 0.44 0.15 0.26 0.29 1.25 27 0.44 0.15 0.27 0.29 1.25 28 0.45 0.14 0.27 0.29 1.25 29 0.45 0.14 0.27 0.29 1.23 20 0.45 0.14 0.20 0.29 1.23 20 0.45 0.14 0.20 0.24 1.11 20 0.44 0.14 0.28 0.24 <td< th=""><th>Dose Level/Sex (mg/kg/day)</th><th>Animal Number</th><th>Body Welght (9)</th><th>Brain</th><th>Heart</th><th>Kidneys L R</th><th>neys R</th><th>Liver</th><th>Lungs</th><th>Spleen</th><th>Testes L</th><th>es R</th></td<>	Dose Level/Sex (mg/kg/day)	Animal Number	Body Welght (9)	Brain	Heart	Kidneys L R	neys R	Liver	Lungs	Spleen	Testes L	es R
32 0.51 0.17 0.28 0.31 1.66 28 0.47 0.18 0.29 0.30 1.29 28 0.45 0.14 0.27 0.32 1.63 26 a0.05 0.16 0.26 0.26 1.18 27 0.44 0.14 0.26 0.25 1.18 25 0.44 0.16 0.26 0.25 1.18 27 0.45 0.15 0.26 0.25 1.18 27 0.45 0.15 0.26 0.25 1.13 27 0.45 0.14 0.27 0.29 1.25 27 0.45 0.14 0.27 0.29 1.25 26 0.43 0.16 0.20 0.29 1.31 26 0.43 0.16 0.28 0.29 1.31 26 0.44 0.14 0.28 0.29 1.31 26 0.43 0.14 0.26 0.26 1.36 27 0.42 0.14 0.29 0.24 <t< th=""><th>305</th><th>61</th><th>27</th><th>0.51</th><th>0.17</th><th>0.30</th><th>0.27</th><th>1.63</th><th>0.18</th><th>90°0</th><th>0.22</th><th>0.25</th></t<>	305	61	27	0.51	0.17	0.30	0.27	1.63	0.18	90°0	0.22	0.25
28 0.47 0.18 0.29 0.30 1.29 28 0.45 0.14 0.27 0.32 1.63 26 a0.05 0.16 0.26 0.26 1.18 27 0.48 0.16 0.26 0.25 1.18 25 0.44 0.16 0.26 0.25 1.18 25 0.44 0.16 0.28 0.29 1.25 27 0.45 0.15 0.26 0.29 1.44 27 0.45 0.14 0.27 0.29 1.25 26 0.45 0.14 0.27 0.29 1.25 27 0.45 0.14 0.27 0.29 1.21 26 0.43 0.16 0.28 0.29 1.31 26 0.44 0.14 0.28 0.27 1.19 27 0.44 0.14 0.28 0.27 1.19 27 0.42 0.14 0.26 0.26 1.36 27 0.42 0.14 0.19 0.27 <t< th=""><th></th><th>62</th><th>32</th><th>0.51</th><th>0.17</th><th>0.28</th><th>0.31</th><th>1.66</th><th>0.17</th><th>0.07</th><th>0.13</th><th>0.13</th></t<>		62	32	0.51	0.17	0.28	0.31	1.66	0.17	0.07	0.13	0.13
28 0.45 0.14 0.27 0.32 1.63 26 a0.05 0.16 0.26 0.26 1.18 27 0.48 0.16 0.36 0.32 1.31 25 0.44 0.16 0.26 0.25 1.18 25 0.43 0.16 0.26 0.25 1.37 27 0.45 0.15 0.26 0.29 1.25 27 0.45 0.14 0.27 0.29 1.25 26 0.45 0.14 0.27 0.29 1.25 26 0.43 0.16 0.20 0.24 1.11 26 0.44 0.14 0.28 0.29 1.31 26 0.44 0.14 0.28 0.29 1.31 26 0.44 0.14 0.28 0.26 1.36 27 0.42 0.14 0.25 0.24 1.17 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 <t< th=""><th></th><th>63</th><th>28</th><th>0.47</th><th>0.18</th><th>0.29</th><th>0.30</th><th>1.29</th><th>0.17</th><th>0.07</th><th>0.18</th><th>0.20</th></t<>		63	28	0.47	0.18	0.29	0.30	1.29	0.17	0.07	0.18	0.20
26 \$0.05 0.16 0.26 0.26 1.18 27 0.48 0.16 0.36 0.32 1.31 25 0.44 0.14 0.26 0.25 1.18 25 0.43 0.16 0.26 0.29 1.25 27 0.44 0.15 0.27 0.29 1.44 27 0.45 0.14 0.27 0.29 1.11 26 0.43 0.16 0.32 0.29 1.31 27 0.47 0.16 0.28 0.29 1.31 26 0.43 0.16 0.28 0.29 1.31 26 0.44 0.14 0.28 0.20 1.36 27 0.44 0.14 0.28 0.27 1.19 26 0.44 0.14 0.28 0.26 1.36 27 0.49 0.14 0.28 0.26 1.36 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.19 0.28 0.29 1.11 27 0.49 0.19 0.28 0.29 1.11		64	28	0.45	0.14	0.27	0.32	1.63	0.18	0.07	0.19	0.20
27 0.48 0.16 0.36 0.32 1.31 25 0.44 0.14 0.26 0.25 1.18 25 0.43 0.16 0.28 0.29 1.25 25 0.45 0.15 0.27 0.29 1.25 27 0.45 0.14 0.27 0.29 1.25 26 0.45 0.13 0.20 0.29 1.25 27 0.45 0.14 0.27 0.29 1.25 26 0.43 0.16 0.28 0.29 1.31 26 0.44 0.14 0.28 0.29 1.31 26 0.43 0.14 0.28 0.29 1.31 27 0.44 0.14 0.28 0.26 1.36 27 0.44 0.14 0.28 0.26 1.36 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.19 0.28 0.26 1.17 27 0.49 0.19 0.29 1.13		9	26	a _{0.05}	0.16	0.26	0.26	1.18	0.19	0.07	0.17	0.16
25 0.44 0.14 0.26 0.25 1.18 25 0.43 0.16 0.28 0.29 1.25 25 0.45 0.15 0.26 0.29 1.25 27 0.44 0.15 0.27 0.29 1.44 27 0.45 0.14 0.27 0.29 1.25 26 0.45 0.13 0.20 0.24 1.11 27 0.47 0.16 0.28 1.23 26 0.44 0.14 0.28 0.29 1.36 26 0.43 0.14 0.28 0.20 1.36 26 0.44 0.14 0.28 0.20 1.36 27 0.42 0.14 0.28 0.26 1.36 27 0.49 0.19 0.27 0.30 1.17 27 0.49 0.114 0.28 0.29 1.11		99	27	0.48	0.16	0.36	0.32	1.31	0.15	90.0	0.18	0.17
25 0.43 0.16 0.28 0.29 1.25 25 0.45 0.15 0.26 0.25 1.37 27 0.44 0.15 0.27 0.29 1.44 27 0.45 0.14 0.27 0.29 1.25 26 0.43 0.16 0.32 0.28 1.23 27 0.47 0.16 0.28 0.29 1.31 26 0.44 0.14 0.28 0.27 1.19 26 0.43 0.14 0.28 0.26 1.36 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.19 0.28 0.29 1.13		67	25	0.44	0.14	0.26	0.25	1.18	0.15	90.0	0.16	0.16
25 0.45 0.15 0.26 0.25 1.37 27 0.44 0.15 0.27 0.29 1.44 27 0.45 0.14 0.27 0.29 1.25 26 0.45 0.16 0.20 0.24 1.11 26 0.43 0.16 0.28 0.29 1.23 27 0.44 0.14 0.28 0.29 1.31 26 0.43 0.14 0.28 0.27 1.19 26 0.43 0.14 0.24 0.26 1.36 27 0.42 0.15 0.25 0.24 1.17 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.19 0.27 0.30 1.31		89	25	0.43	0.16	0.28	0.29	1.25	0.16	90.0	0.16	0.16
27 0.44 0.15 0.27 0.29 1.44 27 0.45 0.14 0.27 0.29 1.25 28 0.45 0.13 0.20 0.24 1.11 26 0.43 0.16 0.28 1.23 27 0.44 0.14 0.28 1.31 26 0.44 0.14 0.28 0.27 1.19 26 0.43 0.14 0.26 1.36 27 0.42 0.15 0.25 0.24 1.17 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.19 0.28 0.29 1.13		69	25	0.45	0.15	0.26	0.25	1.37	0.15	90.0	0.16	0.18
27 0.45 0.14 0.27 0.29 1.25 25 0.45 0.13 0.20 0.24 1.11 26 0.43 0.16 0.28 1.23 27 0.44 0.16 0.28 1.31 26 0.44 0.14 0.28 0.27 1.19 26 0.43 0.14 0.24 0.26 1.36 27 0.42 0.15 0.25 0.24 1.17 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 1.13		7.0	27	0.44	0.15	0.27	0.29	1.44	0.18	90.0	0.19	0.18
25 0.45 0.13 0.20 0.24 1.11 26 0.43 0.16 0.32 0.28 1.23 27 0.44 0.16 0.28 0.29 1.31 26 0.43 0.14 0.24 0.26 1.36 25 0.42 0.15 0.25 0.24 1.17 27 0.49 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 1.13		7.1	27	0.45	0.14	0.27	0.29	1.25	0.18	0.05	0.17	0.16
26 0.43 0.16 0.32 0.28 1.23 27 0.47 0.16 0.28 0.29 1.31 25 0.44 0.14 0.24 0.27 1.19 26 0.42 0.15 0.25 0.26 1.36 27 0.44 0.19 0.25 0.24 1.17 27 0.49 0.14 0.28 0.29 1.30 26 0.45 0.14 0.28 0.29 1.13		72	25	0.45	0.13	0.20	0.24	1.11	0.16	90.0	0.16	0.19
27 0.47 0.16 0.28 0.29 1.31 25 0.44 0.14 0.28 0.27 1.19 26 0.43 0.14 0.24 0.26 1.36 25 0.42 0.15 0.25 0.24 1.17 27 0.44 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 1.13		73	26	0.43	0.16	0.32	0.28	1.23	0.16	90.0	0.17	0.16
25 0.44 0.14 0.28 0.27 1.19 26 0.43 0.14 0.24 0.26 1.36 25 0.42 0.15 0.25 0.24 1.17 27 0.44 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 1.13		74	27	0.47	0.16	0.28	0.29	1.31	0.18	0.07	0.17	0.17
26 0.43 0.14 0.24 0.26 1.36 25 0.42 0.15 0.25 0.24 1.17 27 0.44 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 1.13		75	25	0.44	0.14	0.28	0.27	1.19	0.17	0.07	0.15	0.16
25 0.42 0.15 0.25 0.24 1.17 27 0.44 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 1.13		9/	26	0.43	0.14	0.24	0.26	1.36	0.18	90.0	0.18	0.16
27 0.44 0.19 0.27 0.30 1.30 27 0.49 0.14 0.28 0.29 1.13		11	25	0.42	0.15	0.25	0.24	1.17	0.16	90.0	0.16	0.16
27 0.49 0.14 0.28 0.29 1.13		79	27	0.44	0.19	0.27	0.30	1.30	0.21	90.0	0.20	0.20
316 1 256 0 154		80	27	0.49	0.14	0.28	0.29	1.13	0.12	0.07	0.16	0.17
61:0 0:436 0:02		Mean	26.6	0.456	0.154	0.	0.277	1.315	0.171	0.063	0.	0.173
0.027 0.016 0.029		S.D.	1.7	0.027	0.016	0.	029	0.167	0.015	900.0	0.0	0.023

a = omitted from mean due to suspected erroneous data

0.19 0.16 0.20 0.18 0.18 0.19 0.20 0.20 0.19 0.18 0.19

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0.185 0.017 Testes L R 0.15 0.16 0.19 0.18 0.15 0.17 0.17 0.17 0.19 Spleen 0.062 0.013 0.05 90.0 0.05 0.07 90.0 0.07 90.0 90.0 0.06 90.0 0.179 Lungs 0.15 0.20 0.16 0.18 0.19 0.20 0.19 0.19 0.18 0.17 0.17 0.21 1.363 1.40 Liver 1.40 1.33 1.25 1.32 1.60 1.44 1.32 1.33 1.29 1.28 1.33 1.36 1.41 1.37 0.28 0.30 0.26 0.29 0.29 0.27 0.27 0.28 0.29 0.37 Kidneys L R 0.283 0.25 0.25 0.28 0.29 0.27 0.26 0.29 0.25 0.27 0.27 0.29 0.27 0.25 0.34 0.27 0.159 Heart 0.15 0.15 0.20 0.16 0.16 0.15 0.16 0.16 0.16 0.19 0.16 0.16 0.14 0.14 0.468 Brain 0.48 0.48 0.48 0.46 0.45 0.46 0.48 0.46 0.45 0.47 0.47 0.43 0.47 Body Weight (9) 28.1 29 27 27 27 28 28 28 28 28 28 29 29 29 29 31 31 31 Animal Number Mean S.D. 883 883 884 885 886 887 887 890 990 990 990 990 Dose Level/Sex (mg/kg/day) 753

APPENDIX 11 (continued)

APPENDIX 11 (continued)

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Dose Level/Sex (mq/kq/day)	Animal Number	Body Weight (9)	Brain	Heart	Kidneys L R	leys R	Liver	Lungs	Spleen	Testes L	8 8
2003	101	28	0.49	0.15	0.28	0.32	1.44	0.21	6.07	0.18	0.19
	103	28	0.47	0.15	0.26	0.26	1.47	0.16	90.0	0.18	0.21
	105	25	05.0	0.14	0.23	0.25	1.26	0.17	0.05	0.16	0.16
	109	25	0.49	0.14	0.25	0.26	1.20	0.21	90.0	0.17	0.18
	110	26	0.46	0.14	0.26	0.24	1.16	0.16	90.0	0.18	0.18
	112	27	05.0	0.15	0.28	0.27	1.28	0.20	0.07	0.18	0.18
	114	29*	0.47	0.17	0.29	0.32	1.46	0.21	90.0	0.17	0.17
	Mean S.D.	26.9	0.483	0.149	0.0	0.269	1.324	0.189	0.061	0.0	0.178

* = Animal room body weight

APPENDIX 12

HMX: 13 Week Toxicity Study in Mice Absolute Organ Weights (q) Individual Values - Terminal Sacrifice (Females)

Group/Sex Dose Level	Animal Number	Body Weight (g)	Brain	Heart	Kidneys L R	leys R	Liver	Lung	Spleen
80	121	25	0.49	0.14	0.21	0.22	1.41	0.22	0.09
	122	24	0.46	0.14	0.19	07.0	1.36	0.18	60.0
	123	25	0.45	0.14	0.20	0.19	1.43	0.18	0.09
	124	23	0.46	0.13	0.18	0.19	1.21	0.17	0.08
	125	22	0.43	0.13	0.17	0.17	1.08	0.16	60.0
	126	23	0.46	0.12	0.19	0.20	1.13	0.21	0.07
	127	25	0.44	0.14	0.18	0.22	1.15	0.20	60.0
	128	24	0.47	0.15	0.19	0.21	1.25	0.19	60.0
	129	25	0.47	0.15	0.22	0.22	1.45	0.20	0.08
	130	23	0.43	0.12	0.16	0.17	1.24	0.16	80.0
	132	25	0.48	0.15	0.19	0.21	1.37	0.22	60.0
	133	24	0.49	0.16	0.18	0.20	1.27	0.16	0.09
	134	24	0.42	0.15	0.18	0.21	1.32	0.21	60.0
	135	24	0.44	0.14	0.18	0.19	1.18	0.20	60.0
	136	97	05.0	0.15	0.20	0.21	1.49	0.17	0.09
	137	25	0.45	0.13	0.19	0.17	1.47	0.19	0.08
	138	23	0.46	0.13	0.19	0.17	1.22	0.17	0.08
	139	24	0.47	0.13	0.16	0.18	1.19	0.16	0.07
	140	25	0.48	0.14	0.19	0.21	1.28	0.18	60.0
	Mean	24.2	0.461	0.139	0.	0.192	1.289	0.186	0.085
	s.D.	1.0	0.022	0.011	0.	0.017	0.123	0.021	0.007
		-							

APPENDIX 12 (continued)

Group/Sex Dose Level	Animal Number	Body Welght (q)	Brain	Heart	Kidneys L R	eys R	Liver	Lung	Spleen
801	141	25	0.47	0.15	0.20	0.20	1.36	0.22	0.07
	142	56	0.44	0.13	0.19	0.20	1.48	0.18	0.11
	143	24	0.49	0.14	0.19	0.19	1.29	0.19	0.08
	144	24	05.0	0.15	0.19	0.21	1.37	0.20	0.08
	145	22	0.42	0.13	0.17	0.20	1.21	0.14	0.08
	146	25	0.47	0.14	0.18	0.22	1.24	0.18	80.0
	147	25	0.48	0.14	0.20	0.19	1.37	0.17	0.09
	148	22	0.45	0.15	0.18	0.17	1.26	0.15	0.08
	149	25	0.45	0.14	0.19	0.20	1.35	0.20	0.10
	150	24	0.44	0.15	0.17	0.20	1.28	0.17	60.0
	151	26	0.45	0.14	0.18	0.21	1.40	0.21	60.0
	152	23	0.49	0.13	0.19	0.19	1.14	0.17	0.08
	153	23	0.46	0.15	0.18	0.20	1.19	0.17	0.08
	154	56	0.49	0.14	0.22	0.22	1.25	0.17	60.0
	155	24	0.44	0.15	0.19	0.20	1.23	0.17	0.08
	156	24	0.46	0.15	0.20	0.21	1.37	0.16	0.10
	157	24	0.48	0.13	0.17	0.17	1.26	0.16	0.08
	158	22	0.43	0.12	0.16	0.17	1.16	0.15	0.08
	159	25	0.45	0.14	0.20	0.20	1.28	0.17	0.08
	160	24	0.50	0.14	0.20	0.21	1.33	0.18	0.09
	Mean	24.2	0.463	0.141	0	0.193	1.291	0.176	0.086
	S.D.	1.3	0.024	0.009	•	0.015	0.087	0.020	0.009

APPENDIX 12 (continued)

Group/Sex Dose Level	Animal Number	Body Weight (q)	Brain	Heart	Kidneys L R	eys R	Liver	Lung	Spleen
30%	191	25	0.47	0.14	0.21	0.22	1.40	0.22	0.09
	162	23	0.44	0.13	0.17	0.20	1.15	0.17	60.0
	163	27	0.52	0.15	0.19	0.21	1.50	0.23	0.09
	164	24	0.47	0.12	0.18	0.20	1.21	0.18	60.0
	165	25	0.45	0.13	0.20	0.22	1.37	0.20	0.10
	166	24	0.43	0.15	0.18	0.19	1.35	0.19	60.0
	167	25	0.45	0.15	0.20	0.22	1.45	0.19	0.09
	169	25	0.48	0.16	0.18	0.20	1.34	0.18	0.11
	170	25	0.47	0.14	0.19	0.18	1.22	0.17	0.08
	171	24	0.46	0.14	0.19	0.20	1.23	0.17	0.08
	172	24	0.45	0.14	0.20	0.20	1.30	0.23	0.08
	173	56	0.48	0.15	0.19	0.21	1.47	0.17	0.09
	175	25	05.0	0.15	0.20	0.22	1.35	0.16	0.08
	374	25	0.47	0.15	0.21	0.22	1.28	0.20	60.0
	176	24	0.45	0.14	0.18	0.20	1.52	0.19	0.10
	177	56	0.48	0.15	0.18	0.21	1.40	0.20	60.0
	178	25	0.47	0.13	0.18	0.18	1.22	0.16	0.09
	179	24	0.46	0.14	0.20	0.20	1.35	0.16	0.08
	180	26	0.47	0.14	0.19	0.22	1.33	0.23	60.0
	Mean	24.8	0.467	0.142	0.	0.198	1.339	0.189	0.089
	S.D.	1.0	0.021	0.010		0.014	0.104	0.024	0.008

APPENDIX 12 (continued)

Group/Sex Dose Level	Animal Number	Body Weight (q)	Brain	Heart	Kidneys L R	leys R	Liver	Lung	Spleen
806	181	22	0.47	0.12	0.16	0.18	1.19	91.0	0.07
	182	23	0.45	0.12	0.19	0.19	1.19	0.18	60.0
	183	23	0.46	0.12	0.18	0.19	1.32	0.15	60.0
	184	22	0.45	0.13	0.18	0.21	1.25	0.16	0.08
	185	24	0.46	0.13	0.19	0.20	1.28	0.18	0.09
	186	23	0.46	0.13	0.18	0.20	1.19	0.22	0.09
	187	25	0.48	0.14	0.19	0.19	1.41	0.17	0.08
	188	24	0.45	0.12	0.17	0.20	1.33	0.17	0.08
	189	24	0.47	0.13	0.18	0.18	1.30	0.19	0.08
	190	27	0.46	0.14	0.20	0.21	1.51	0.23	0.09
	191	27	0.50	0.15	0.18	0.20	1.48	0.19	0.09
	192	21	0.47	0.13	0.15	0.17	1.16	0.18	0.08
	193	24	0.46	0.14	0.19	0.18	1.24	0.19	60.0
	194	23	0.46	0.13	0.17	0.18	1.34	0.16	0.07
	195	26	0.46	0.14	0.19	0.20	1.38	0.20	0.09
	196	25	0.50	0.14	0.19	0.21	1,35	0.16	0.08
	197	24	05.0	0.14	0.18	0.20	1.41	0.15	0.08
	198	24	0.47	0.14	0.18	0.19	1.20	0.17	60.0
	199	23	0.42	0.13	0.20	0.19	1.25	0.18	0.10
	200	24	0.47	0.13	0.21	0.21	1.45	0.23	60.0
	Mean	23.9	0.466	0.133	0.	0.184	1.312	0.181	0.085
	s.D.	1.6	0.019	600.0		0.024	0.104	0.024	0.008

APPENDIX 12 (continued)

Group/Sex Dose Level	Animal Number	Body Welght (9)	Brain	Heart	Kidneys L R	eys R	Liver	Lung	Spleen
250%	202	24	0.46	0.13	0.18	0.18	1.09	91.0	90.0
	203	56	0.48	0.15	0.20	0.21	1.66	0.18	0.08
	205	56	0.46	0.14	0.20	0.22	1.70	0.18	0.08
	209	25	0.48	0.14	0.19	0.19	1.27	0.16	0.07
	212	25	0.48	0.15	0.19	0.19	1.25	0.16	60.0
	213	24	0.47	0.12	0.18	0.19	1.46	0.22	80.0
	214	26	0.53	0.14	0.20	0.19	1.26	0.18	0.07
	220	27	0.57	0.15	0.19	0.22	1.40	0.18	0.09
	Mean S.D.	25.4	0.491	0.140	0.	0.195	1.386	0.178	0.078

APPENDIX 13

HMX: 13 Week Toxicity Study in Mice Gross Pathology and Histopathological Findings for Individual Animals

Abbreviations used in these reports:

NAD = No abnormality detected.

TK = Terminal kill.

FD = Found dead.

KIE = Killed in extremis.

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Tip of tail missing from Week 4.		NAD.			Klaneys Perirenal fat	P
					Lungs	Γ
					Heart	E
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					Thymus	\pm
					MUSCIP Calivary Cl	Ŀ
					SM Lymph N	Ŀ
					Pancreas	
					Trachea	3
					Thyroids	3
					Parathyroids	9
					Oesophagus	\overline{H}
					Stomach	H
Necropsy Findings					Duodenum	\pm
					Ileum	1
					Je junum	F
NAD.					Caecum	4
					Colon	1
					Rectum	1
				_	Mesenteric LN	1
					Aorta	ŀ
				-	Adrenais	}
	•				Bronchial	,
					lestes	1
					Prostate	1-
					Pituitary	ŀ
					Bladder	Ŀ
					Skin	-
					Mammary Gl	1
					Eyes	7
					Brain	4
					Spinal cord	9
					Sternum	
					Nares	_
					Sciatic nerve	<u>1</u>
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	Number of	Sections Examined			Liver Kidneys	Lunds	Heart	Spleen	Thymus	Salivary Gl	SM Lymph N	Pancreas	Traches	Parathyroids	Oesophagus	Stomach	Duodenum	Telim	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals Bronchial IN	Testes	Prostate	Pituitary	Bladder	Skin	manmary G1	Eyes	Brain Criss and	Sternim	Nares	Sciatic nerve	
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	Number of Sections Examined			Liver	Perirenal fat	Lunds	Heart	Spiren	Muscle	Salivary Gl	SM Lymph N	Pancreas	Thurnide	Parathyroids	Oesophagus	Stomach	Duodenum	Ileum	Jejunum	Caecum	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Testes	Pituitary	Bladder	Skin	Mammary G1	Eyes	Brain	DIO TRITICO	Nares	Sciatic nerve		
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Time on Study	14				NAD.																															~ ==	
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Clinical History						뷮
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					Trachea	Н
				4	Thyroids	4
				Pa	Parathyroids	9
				<u>*</u>	Oesophagus	1
		_		<i>t.</i>	Stomach	1
Necropsy Findings				D	Duodenum	1
finance Indonesia				11	lleum	1
				Je	Jejunum	<u>d</u>
NAD.		-		<u>8</u>	Caecum	1
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Project No: 416877 Group: 1 Centrol		Time on Study	Death			
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Animal No: 14 Sex: Of		14	TK	<u> </u>	Number of Sections Examined	ed
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Clinical History	Sample		Histopathology			
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					Trachea	$\overline{+}$
					Thyroids	7
					Parathyroids	9
					Oesophagus	7
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Necropsy Findings				_	Duodenum	\exists
					Ileum	7
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NAD.					Caecum	$\overline{+}$
				<u> </u>	Colon	\overline{A}
					Rectum	\overline{A}
					Mesenteric LN	-1
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Project No: 416877 Group: 1 Control		Time on Study	Death			ſ
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Project No: 416877 Group: 1 Control	Animal No: 16 Sex: O		Clinical History		NAU.											Necropey Fludings	chirpura Indonesia		NAD																

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Phyroids Parachyvoids Geophaus Strenach Bucdenun Jujuum Caecum Colon Rectum Retenteric IA Adrenals Retenteric IA A						Trachea	上
Necropsy Findings Necropsy Findings Necropsy Findings Necropsophaus Stonach Stonach Stonach Stonach Stonach Acrea section Resenteric LN Acr						Thyroids	1
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Necropsy Findings Necropsy Findings Secure Duodenum Iteum Cacium Cacium Cacium Rectum Rectum Resenteric LM Adrenals Bronchial LM Pitultary Blader Skin Skin Spinal cord Sterum Nares Sciatic nerve						Oesophagus	1
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Colon Rectum Resenteric LN Aorta Aor						Jejunum	1
Colon Rectum Mesenteric IN Aorta Adrenals Bronchial IN Testes Prostate Pituitary Bladder Skin Hammary Gl Eyes Brain Spinal cord Sternum Nares Sciatic nerve	NAD.					Caecum	1
Rectum Resenteric IN Aorta Adrenals Bronchial IN Testes Prostate Pituitary Bladder Skin Mammary Gl Eyes Brain Spinal cord Sternum Nares Sciatic nerve						Colon	4
Mesenteric LN Agrenals Adrenals Adrenals Bronchial LN Testes Prostate Pituitary Bladder Skin Mammary Gl Eyes Brain Spinal cord Sternum Nares Sciatic nerve						Kectum	1
Adrenals Recordial LN Testes Prostate Prostate Pituitary Bladder Skin Mammary Gl Eyes Brai Spinal cord Sternum Nares Sciatic nerve						Mesenteric LN	Ŀ
Adrenals Bronchial LW Testes Prostate Pituitary Bladder Skin Marmary Gl Eyes Brain Spinal cord Sternum Nares Sciatic nerve						Aorta	Ŀ
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nd cord						Mammary Gl	임
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0						Brain	4
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		Number of Sections Examined			Liver	Kidneys	Perirenal fat	Lunds	Heart	Thymne	Musc lo	Salivary Cl	SM Lymph N	Pancreas	Trachen	Thyroids	Parathyroids	Oesophagus 6.	Stomach	11eum	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenais Bronchial LN	Toctoc	Prostate	Pituitary	Bladder	Skin	Mammary Gl	Eyes	Brain	Spinal cord	Sternum	Nares	Sciatic nerve		
p, Study Death	CAN D	4 TK		Histopathology																																					
Time Shudy		14				NAD.												_																							
				Sample																							•														
Group:	Project No: 416877 Group: 1 Control Animal No: 20 Sex: O			Clinical History		NAD.													No. of the State o	vectopsy runnings		NAD.																			

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Project No: 416877 Group: 2 5 mg HMX/kg/day	g/day	Time on Study	Death		ļ	
Animal No: 21 Sex: of		14	TK		Number of Sections Examined	J. Page
						보
Clinical History	Sample		Histopathology	,		╀┦
NAD.		NAD.			Liver Kidneys	212
					Brain	Ti
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Necropsy Findings						
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Project No: 416877 Group: 2 5 mg HMX/kg/day	kg/day	Time on Study	Death			1
Animal No: 22 Sex: đ		14	TK		Number of Sections Examined	P
						보
Clinical History	Sample		Histopathology			Ш
NAD.	Liver	Several foci ly	Several foci lymphocytes and polymorphs.	ymorphs.	Liver Kidneys Spleen Brain	44-6
				7		
Necropsy Findings		-				
NAD.						
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	Number of Sections Examined	扭		s.	Brain 3		- 						_1_
Death	TK		Histopathology										
Time on Study	14			NAD.									
/kg/day			Sample								•		
Project No: 416877 Group: 2 5 mg HMX/kg/day	Animal No: 23 Sex: G		Clinical History	NAD.				 Necropsy Findings	NAD.				

		nined	빞	ŀ	
	Number of	Sections Examined			Liver Spleen Brain
_	Γ	_		logy	
Death		Ϋ́		Histopathology	
Time on Study		14			NAD.
(d/day				Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/day		24 sex:		Clinical History	NAD.

ned	벍		
Number of Sections Exami			Liver Skidneys Spleen Brain
		У	
ТK		Histopatholog	
14			NAD.
		Sample	•
Animal No: 25 Sex: of		Clinical History	NAD.
	25 Sex: O 14 TK	25 Sex: O J4 TK Sections Examin	25 Sex: O Number of Sections Examin Clinical History Sample Histopathology

	ined	보		44-6		Ш	Ш			Ш	Ш	Ш	Ш	Ш	Ш	Ц.	Ц	Ш
	Number of Sections Examined			Liver Kidneys Spleen	brain													
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		7	Υt															
Death	ΤX		Histopathology			•												
			H1S															
Time on Study	14			NAD.														
lay			Sample					·				•	-					
mg HMX/kg/day						 		 	T	 								
Group: 25 mg H	_		story					dinas										
			Clinical History					Necropsy Findings										
Project No: 416877	Animal No: 26			NAD.					4 2 2									

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	Number of Sections Examined		Liver Kidneys Spleen Brain
		.	
Death	TK	Histopathology	
Time on Study	14		NAD.
(g/day		Sample	•
Group:	27 Sex: o	Clinical History	Necropsy Findings
	Animal No:		NAD.

	Number of Sections Examined	뷮		Kidneys 2 Spleen 1		Ш					·	<u> </u>		<u> </u>		<u> </u>	·	·					<u></u>			
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																						,	•		•	
Death	ТK		Histopathology																							
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Time on Study	14			Not examined.																						
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5 mg HMX/kg/day			Sample	Bladder			_											•	•	•	•	•	•	•	•	•
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_	Sex: of		Istory									seulput	undings.	Indings	indings	Indings	indings	'indings	indings	Indings	indings	'indings	'indings	Indings	lndings	'indings
			Ciinical History									Necropsy Findings	Necropsy F.	Necropsy F.	Necropsy F.	Necropsy F:	Mecropsy F:	Vecropsy F:	Vecropsy F:	Recropsy F:	Mecropsy F.	ended.	Wecropsy F.	rended.	ended.	rended.
	Animal No: 28			٥.									adder dist	Necrops Bladder distended.	adder dist	adder dist	adder dist	adder dist	adder dist	adder dist	adder dist	adder dist	adder dist	adder dist	adder dist	adder dist
Proje	Antma			NAD.		_		·	·				33.	818	в1а	ВЪ	ВЪ	Bla	Bla	Bla	ВІа	в1а	Bla	B1a	В1а	B1a

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	Number of Sections Examined		Liver Kidneys Spleen Brain
		71	·
Death	TK	Histopathology	
Time on Study	14		NAD.
kg/day		Sample	•
: 416877 Group	Animal No: 29 Sex: of	Clinical History	NAD.

	3	보	ľ	
	Number of Sections Examined			Liver Kidneys Spleen Brain
			λ	
Death	T.		Histopathology	
Time on Study	14			NAD.
>eD/Da			Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/dav	Sex: O		Clinical History	Necropsy Findings NAD.

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		Number of Sections Examined			Liver Kidneys Spleen	Brain		<u>-</u>															
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Death		ТK		Histopathology																			
Time on Study	100000	14			NAD.																		
ka/dav	[n / 6 .	_		Sample														•					
Project No: 416877 Group: 2 5 mg HMX/kg/day		Animal No: 31 Sex: O		Clinical History	NAD.								Necropsy Findings	NAD.									

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	Number of Sections Examined		Liver Kidneys Spleen Brain
Death	ТК	Histopathology	
Time on Study	14		NAD.
kg/day		Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/day	Sex: O	Clinical History	Necropsy Findings D.
Proje	Anima		NAD.

Project No: 416877 Group: 2 5 mg HMX/kg/day	g/day	Time on Study	Death			
Animal No: 33 Sex: O		14	ŢK		Number of	
				_	Sections Examined	E E
Clinical History	Sample		Histopathology	٨		╀┸
NAD.		NAD.			Liver Kidneys Spleen Brain	2/7-m
						444
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Necropsy Findings						11
NAD.	•					<u></u>

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	Number of	Sections Examined		Liver Kidneys Spleen Brain
				·
Death		TK	Histopathology	
Time on Study		14		NAD.
day		 -	Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/day	, A	34 065.	Clinical History	Necropsy Findings NAD.

	ne d	뷮		
ı	Number of Sections Examined			Liver Spleen Brain
			٨	
Death	TK		Histopathology	
Time on Study	14			NAD.
kg/đay			Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/day	Sex: Q		Clinical History	Necropsy Findings NAD.

	ined	보		
	Number of Sections Examined			Liver Kidneys Spleen Brain
Time on Study Death	14 TK		Histopathology	MAD.
L	 -		Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/day	Sex: o		Clinical History	NAD.

	P G		
	Number of Sections Examined		Liver Kidneys Spleen Brain
		^	-
Death	ТК	Histopathology	
Time on Study	14		NAD.
'day	,	Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/day	Sex: o	Clinical History	NAD.

	Ined	보	ŀ	
	Number of Sections Examined			Liver Spidneys Spidneys Brain
			hology	
Death	TK		Histopathology	
Time on Study	14			NAD.
d/dav			Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/dav	Sex: o		Clinical History	NAD.

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	Number of Sertions Frances	The state of the s		Liver Kidneys Spleen Brain		 	
		7	logy				
Death	Ϋ́Т		Histopathology				
Time on Study	14	7		NAD.			
kg/day			Sample				•
Project No: 416877 Group: 2 5 mg HMX/kg/day	Sex: o		Clinical History	NAD.		Necropsy Findings	MAD.

	Ined	벋	Ţ	
	Number of Sections Examined			Liver Skidneys Skidnen Brain
			Histopathology	
Death	ΑŢ		Histopa	
Time on Study	14			NAD.
ka/dav			Sample	•
Project No: 416877 Group: 2 5 mg HMX/kg/dav	Sex: O		Clinical History	NAD.

	Ped	뷮		
	Number of Sections Examined			Livor Kidneys Spleen Brain
Ę			Histopathology	
Death	ŢŢ		Histop	
Time on Study	14			NAD.
/kg/day			Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	4		Clinical History	NAD.

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i	Number of Sections Examined		Liver Kidneys Spleen Brain
Death	ТК	Histopathology	
Time on Study	14	H	NAD.
/kg/day		Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Animal No: 42 Sex: of	Clinical History	Necropsy Findings NAD.

ned T		
Number of Sections Examined		Liver Kidneys Spleen Brain
dy Death	Histopathology	
Time On Study		NAD.
/kg/day	Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day Animal No: 43 Sex: O	Clinical History	NAD.

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	Number of Sections Examined		Liver	Spleen			 			 			<u> </u>			
Death	TK	Histopatho]ogv	The state of the s													
Time on Study	14								·-							
/kg/day		Sample									•					
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: O	Clinical History	NAD					Necropsy Findings	NAD.							

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	Number of Sections Examined			Liver Kidencys Spieen Brain
	Γ-	,	46	
Death	TK		Histopathology	•
Time on Study	14			NAD.
/kg/day			Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: O		Clinical History	NAD.

	P		
	Number of Sections Examined		Liver Kidnoys Spleen Brain
		эду	
Death	TK	Histopathology	
Time on Study	14		NAD.
/kg/day	•	Sample	•
Protect No: 416877 Group: 3 12 mg HMX/kg/day	Sex: O	Clinical History	NAD.

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	Number of Sections Examined		Liver Kidneys Spleen Brain
Death	TK	Histopathology	
Time on Study	14		NAD.
/kg/day		Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Animal No: 47 Sex: O	Clinical History	NAD.

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	Number of	Sections Examined		1,6004	Kidneys	Spleen	Brain				_												_			
Death	Ţĸ		Histopathology										•													
Time on Study	14				NAD																					
/kg/day			Sample																•							
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: O		Clinical History		NAD.								Necropsy Findings		NAD.										•	

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	Number of Sections Examined		Liver Kidneys Spleen Brain
		X	·
Death	TK	Histopathology	•
Time on Study	14		NAD.
/kg/day		Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	49	Clinical History	Necropsy Findings
Project A	Animal No:		NAD.

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	Number of Sections Examined		Liver Kidneys Spleen Brain			
Death	TK	Histopathology				
Time on Study	14		NAD.			
/kg/dav		Sample				•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: O	Clinical History	NAD.		Necropsy Findings	NAD.

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	Number of Sections Examined			Liver	Spleen		_	-														
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Death	TK		Histopathology									•										
Time on Study	14			Can	•	-																
/kg/day			Sample													•		_				
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: o		Clinical History	NAD.								Necropsy Findings	. Com									

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	Number of	פררוסוו באפו		Liver Kidncys Spleen Brain
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Death	*		Histopathology	
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Time on Study	14			NAD.
/kg/day			Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: O		Clinical History	Necropsy Findings NAD.

NAD. Sant Animal No. Sant Animal No. Sant Animal No. Sant Animal No. Sant Animal National	Project No: 416877 Group: 3 12 mg HMX/kg/day	/kg/day	Time on Study	Death			
Mecropsy Findings NaD.	53 Sex :		14	TK		Number of	
Clinical Mistory Sample Mistopathology Liver Material Manage NAD. NAD. Manage Spieen					-	THE SHOTTERS	벌
NAD. Spleen Kldvys Spleen Sple	Clinical History	Sample		Histopathology			
Necropay Findings Necropay Findings	NAD.		4			Liver	7
Necropsy Findings			NAD.			Spleen	1
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	Number of Sections Examined		Liver Kidneys Spleen Brain
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Death	TK	Histopathology	-
Time on Study	14		NAD.
/kg/day		Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: o	Clinical History	NAD.

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	Number of Sections Examined		Liver Kidneys Spleen Brain
	 1	yę	
Death	TK	Histopathology	·
Time on Study	14		NAD.
kg/day		Sample	•
: 416877 Group: 3 12 mg HMX/kg/day	55 Sex: 0	Clinical History	Necropsy Findings
Project No: 416877	Animal No:		NAD.

	D E		
	Number of Sections Examined		Liver Kidneys Spleen Brain
		٨	
Death	TK.	Histopathology	<u>-</u>
Time on Study	14		NAD.
/kg/day		Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: O	Clinical History	NAD.

Histopathology Four polymorphs. Red and white pulp depletion. Hamber of Sections Examin Brain Brain Four polymorphs.	Pred Section 1.1v
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	P S		
	Number of Sections Examined		Liver Kadneys Spleen Brain
		٨	
Death	Ţĸ	Histopathology	·
Time on Study	14		NAD.
/kg/day		Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day		Clinical History	NAD.

	ned	보		
	Number of Sections Examined			Liver Spiderys Brain
			γ	
Death	TK		Histopathology	
Time on Study	14			NAD.
/kg/day			Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Animal No: 59 Sex: đ		Clinical History	NAD.

	Ined	벌	Ĭ	
	Number of Sections Examined			Liver Kidhocys Spleen Brain
			у	
Death	TK		Histopathology	
Time on Study	14			NAD.
/kg/day			Sample	•
Project No: 416877 Group: 3 12 mg HMX/kg/day	Sex: G		Clinical History	NAD.

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	Number of	Sections Examined			Liver	Kidneys Perfrenal fat	Lange	Heart	Spleen	Тһутыя	Muscla	Callyary Cl	Pancreas	Trachea	Thyroids	Parathyroids	Oesophagus	Diodonim	11cm	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Testes	Prostate	Bladder	Skin	Mammary Gl	Eyes	Brain	Spinal cord	Sternum	Crist (n porto	1	
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Death		ТК		Histopathology																																			
Time on Study		14				NAD.																									_								
(/kg/dav	Inn/hu/			Sample																								•											
DECISE NO. 416877 Group. 4 30 mg HMX/kg/dav	F 40	Animal No: 61 Sex: U		Clinical History		CAN													Necropsy Findings		CVX	- Own																	

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	Number of	Sections Examined		Liver	Kidneys	Lange	Heart	Spleen	Thymus	Salivary Cl	SM Lymph N	Pancreas	Thurnide	Parathyreids	Oesophadus	Stemach	Duodenum	Treum	Je junum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Testes	Pituitary	Bladder	Skin	Mammary Gl	Eyes	Brain	Spinal cord	Sternum	Sciatic nerve			
		-		997																																		
Death	Ä	T.Y	Jod + enc + a tu	nistopathology																																		
Time on Study	:	14			NAD.																																	
(/kg/day			1	Sample																					_	•												
Project No: 416877 Group: 4 30 mg HMX/kg/day	Sex: O			Clinical History	Q. A. Z.												Necropsy Findings		NAD.																			

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	Number of Sections Examined			Liver Efdneys	Perfrend for	Lungs	Select	Thymas	Muscle	Salivary Gl	Panereas	Trachea	Thyroids	Parathyroids	Oesophagus Stomach	Duodenum	Ileum	Jejunum	Caecum	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Prostate	Pituitary	Bladder	Skin	Mammary GI	Brain	Spinal cord	Sternum	Nares	Sciatic nerve		
Death	TK		Histopathology																																	
Time on Study De	14		Histo																																	
L	L]	Sample		NAD.				-															•							_					
Project No: 416877 Group: 4 30 mg HMX/kg/day	Sex: O		Clinical History		NAD.											Necropsy Findings	The state of the s		NAD.																	

Project No: 4164// Group: 4 30 mg HMX/kg/day	/kg/day	Time on Study	Death	•		
O .xes					Number of	
		14	TK		Sections Examined	P
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Clinical History	Sample		Histopathology	,		\sqcup
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					Muscle	1
					Salivary Cl	1
					SM Lymph N	1
					Pancreas	ユ
					Trachea	1
				•	Thyrolds	1
					Parathyroids	9
					Oesophagus	1
Noncomon Eladina					Stomach	9
necropsy rangings					Duodenum	1
					I leum	1
NAD.					Jejunum	1
					Caecum	1
					Colon	1
					Rectum	1
					Mesenteric LN	٠.
					Aorta	1
					Adrenals	Ŀ
	•				Bronchial LN	1
					Testes	1
					Prostate	1
					Pituitary	4
					Bladder	1
					Skin	4
					Mammary Gl	<u>d</u>
		•			Eyes	1
					Brain	
					Spinal cord	4
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	Number of	-St			Liver	Kidneys Perirenal fat	Lungs	Beart	Spleen	Thymus	Salivary Cl	SM Lympth 17	Pancreas	Trached	Thuroids	141.4.19.16.10.3	Oesophagus Stomach	Dvodenum	Ileum	Jejunum	Carcum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Testes	Prostate	Fituitary	Bladder	Skin	Free C	Brain	Spinal cord	Sternum	Nares	Sciatic nerve		
				ıy																																			
Death		ТK		Histopathology																																			
Time On Study	(WEEKS)	14				NAD.																																	
	(/kg/day			Sample												-											•								,				
!	Project No: 4168// Group: 4 30 mg HMX/kg/day	Animal No: 65 Sex: of		Clinical History		NAD.													Necropsy Findings		NAD.																		

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	Number of	10000		Liver	ridneys Perirenal fat	Shurd	Heart	Stleen	Thymas	Salivary Gl	S. Lymph N	Pancreas	Thursids	Parathyroids	Oesophagus	Stomach	Duodenum	Tojum	E 10 40	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Testes	Prostate	Pituitary	Bladder	Skin	Charactery CI	Lyes	Spinal cord	Sternum	Nares	Sciatic nerve		,
		- -	٨																																		
Death	TK		Histopathology																																		
Time on Study	14				NAD.																										-						
K/kg/day			Sample																						•												
Project No: 416877 Group: 4 30 mg HMX/kg/day	Animal No: 66 Sex: o		Clinical History		NAD.												Necropsy Findings		NAD.																		

	Γ	P	벋	Ī	7-	F	-	4	F	7	Ţ-	E	4	F	4	E	Ŧ	$\overline{\mathbb{F}}$	\mathbb{I}	Ŀ	ŀ	Ŀ	Ŀ	E	Э	۲	$\overline{\mathbb{F}}$	4	ŀ	Ŀ		d	-	4	3	_	_]	╧	1	4
	Number of	Sections Examined			Liver	nadamys Perirenal fat	Lungs	Heart	Spleen	Thymus	Muscher	CM Lymph N	Pancreas	Traches	Thyroids	Parathyroids	Oesophagus	Stomach	Duodenum	E110-11	Jejunum	Caecum	Restu	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Testes	Prostate	Pittirary	Skin	Mammary Gl	Eyes	Brain	Spinal cord	Sternum	Nares	Sciatic nerve			
	T-			17																																					
Death		TK		Histopathology																																					
Time on Study	(CYCLM)	14		; ;		NAD.																																			
246/04/	// Ay/ udy			Sample								_															•								•						
, de	dno io	Animal No: 67 Sex: 0		Clinical History		NAD.													Necropsy Findings			NAD.																			

Project No: 416877 Group: 4 30 mg HMX/kg/day	(/kg/day	Time on Study	Death		
Sex:	•	, ,	à E	Number of	
	-	4	T.Y	Sections Examined	ned
					HE
Clinical History	Sample		Histopathology		
				Liver	1
NAD.		NAD.		Kidneys	_
				rerirenal tat	1
				Lungs	1
				Beart	\mathbb{F}
				Spleen	1
				Thymus	1
				Muscle	\exists
				Salivary Gl	E
				SM Lymph N	<u>H</u>
				Pancreas	1
				Trachea	\exists
				Thyroids	?
		-		Parathyreids	\exists
				Oesophagus	\exists
				Stomach	4
Necropsy Findings				Duodenum	\exists
				Ileum	4
CAZ				Jejunum	ط
				Caecum	5
				Colon	-
				Rectum	4
				Mesenteric LN	4
				Aorta	4
				Adrenals	1
				Bronchial LN	4
	•			Testes	٦
				Prostate	4
				Pituitary	4
				Bladder	4
		-		Skin	4
				Mammary Gl	þ
				Eyes	٦
				Brain	4
				Spinal cord	~
				Sternum	_
				Nares	
				Sciatic nerve	

Project No: 416877 Group: 4 30 mg HMX/kg/day	X/kg, day	Time on Study	Death	Ĺ		ſ
Sex: O		14	ЛK	_ š	Number of Sections Examined	٩٩
						HE
Clinical History	Sample		Histopathology			
		4-3 g	0 0 0 0 0 0 0 0 0 0	1 X	Liver Kidneys	$\exists \exists$
NAD.	Brain	Focus of fat ce	rocus of fat cells in ventricle.	<u>~</u>	Perirenal far	Ŧ
				<u> </u>	Lungs Heart	-
				<u> </u>	Spideen	F
				F :	Thymus	4
				<u> </u>	Muscle Saliwary Gl	-
-				ά τ.	SM Lymph N	19
				-	Sancreas	\exists
				E	Trachea	\exists
				-	Thuroids	-
				<u> </u>	Parathyroids	4
				Ŏ	Oesophagus	1
				v. č	Stomach	1
Necropsy Findings					Themm	Ŀ
				-	Jejunum	1-
				0	Caecum	-
NAD.					Colon	Н
				Ř	Rectum	\forall
	<u>-</u>			<u>x</u>	Mesenteric LN	4
				Ř.	Aorta	1
				Ă.	Adrenals	ئا-
	1			<u> </u>	Bronchial LN	ſ
				- 6	Testes	10
				-	Pituitary	Ы
				<u> </u>	Bladder	占
				į.	Skin	4
				Σ	Mammary Gl	4
		•		ei	Eyes	1
				<u> </u>	Brain	7
				S	Spinal cord	7
				<i>y</i> 2	Sternum	Ŀ
				S	Sclatic nerve	<u> </u>
						4

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	Number of Sections Examined			Liver	Perfress fat	Lunds	Heart	il-Teon	Thymus Muscle	Salivary Gl	SM Lymph N	Fancreas Trachea	Thyroids	Parathyreids	Overophania	Stomach	Duodenum	Totalita	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Pronchial LN	Testes	Pituitary	Bladder	Skin	Mammary G1	Eyes	Brain	Spinal cord	Sternum	Sciatic nerve	
		-	٨																													-				
Death	TK		Histopathology																																	
Time on Study	14			NAD.	•																															
x/kg/day			Sample		_																				•											
Project No: 416877 Group: 4 30 mg HMX/kg/day	Animal No: 70 Sex: of		Clinical History	NAD.												Month of Parties	Necropsy ringings		NAD.																	

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	Number of Sections Examined			Liver	Perfrenal fat	Lungs	Heart	Spleen	Thymas	Salivary 61	SM Lymyth N	Pancreas	Thereids	Parathyroids	Oesophagus	Stomach	Duodenum	Jelunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals Brouchial LN	Testes	Prostate	Pituitary	Bladder	Mannary Cl	Fyng	Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
		7	уфс																																	
Death	Ţ		Histopathology																																	
Time on Study	14				NAD.																															
x/kg/day			Sample																						•											
Project No: 416877 Group: 4 30 mg HMX/kg/day	Animal No: 71 Sex: of		Clinical History		NAD.												wecropsy rangings		NAD.																	

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	Number of	Sections Examined			Liver	Kidneys	Turis Indian	Spund.	Heart	E 0 7 1	Thymus	Salivary Gl	SM Lymp's N	Pancreas	Trachea	Thyroids	Parathyroids	Oesophagus	Stomach	Duodenum	Ileum	Jejunum	Caecum	Colon	Rectum	Mesenceric LA	Advenale	Bronchial LN	Testes	Prostate	Pituitary	Bladder	Skin	Mammary G1	Eyes	Brain	Spinal cord	Sternum	Nares	Sciatic nerve			
				ıy																																							
Death		Ţĸ		Histopathology																																							
Time on Study		14				NAD.																													•								
K/kg/day				Sample																									•														
Project No: 416877 Group: 4 30 mg HMX/kg/day	٠, ٥٥	: xex : 7/		Clinical History		NAD.														Necropsy Findings			• Gran																				

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	Number of Sections Examined			Liver	Perfectal fat	Lunds	Reart	U.O. F. J.	Muscle	Salivary Gl	N Hyper Mc	Trachea	Thereids	Parathyroids	Ocsophagus	Stenach	ED FLOOR	Jojunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Bronchial LN	Testes	Prostate	Pituitary	Income in	Manmary G	E).es	Brain	Spinal cord	Sternum	SOLEX.	Sciatic nerve		
Death	TX		Histopathology																																		
Time on Study	14				. NAD.																																
K/kg/day	•		Sample									_													•										_		
Project No: 416877 Group: 4 30 mg HMX/kg/day	Sex: O		Clinical History		NAD.												Necropsy Findings		NAD.																		

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	Number of	Sections Examined		Liver	Kidneys	Perirenal fat	Lunds	Heart	Spleen	Thymus	Muscle Caldustic	SM Lymph N	Pancreas	Trachea	Thyreids	Parat hyroids	Oceophagus	Stomach	Duodenum	Eno11	Jejunum	Caecum	Restum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Testes	Prostate	Pituitary	Skin	Mammary G1	Eyes	Prain	Spinal cord	Sternum	Nares	Sciatic nerve	
		7	ology																																				
Death	Ě	\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	Histopathology																																				
Time on Study	9 (NAD.																											•						
30 mg HMX/kg/dav	•		Sample									-																•											
Project No: 416877 Group: 4 30 mg HM	Sex: o		Clinical History			NAD.													Necropsy Findings			NAU.																	

Group: 4 30 mg HMX/kg/day
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	Number of	Sections Examined			Liver	Kidneys Perirenal fat	Lunds	Heart	Spleen	Тһутиѕ	Muscle Cellinami Ci	Salivary GI	Pancreas	Trachea	Thyroids	Parathyreids	Oesophagus	Scomacn	Duodenum	To summer	Or Junean	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Testes	Prostate	Pituitary	Diagonal di	Skin Mammary G	Free Co.	Brain	Spinel cord	Sternum	Nares	Sciatic nerve	
				Ą£																																	_		
Death		TK		Histopathology																																			
Time on Study		14				NAD.																																	
K/kq/day		•		Sample																								•											
Project No: 416877 Group: 4 30 mg HMX/kg/day	Sex:	. O .		Clinical History		NAD.													Necropsy Findings		NAD																		

Project No: 416877 Group: 4 30 mg HMX/kg/day	X/kg/day	Time on Study	Death			
Sex: O		14	TK		Number of Sections Examined	ned
						HE
Clinical History	Sample		Histopathology			
		1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	4	2 1 6 20 0	Liver	<u>-</u> ^
NAD.	ьуе	only one normal	only one normal eye present on silues:	· santis	Perirenal fat	ш
					Lunds	1
					Seleen	1
					Thymus	1d
					Muscle	Ц
					Salivary Gl	1
					N Hymyl M.	1
					Pancreas	1:
					Traches	1
					Thyrolds	C
					Parathyreids	1
					Ocsophagus	1
					Stomach	1
Necropsy Findings					Therm	90
					Tire to the	1-
Right eve small and shrivelled up in					Caecum	1
socket.					Colon	
					Rectum	Ц
					Mesenteric LN	ā
					Aorta	1
					Adrenals	7
					Bronchial LN	4
	•				Testes	4
					Prostate	1
					Pituitary	1:
					Skin	ــا
					Manamary G1	d
					Eyes	
					Brain	
					Spinal cord	7
					Sternum	_1
					Narcs	_
					Sciatic nerve	0
						1
						┨

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	Number of Sections Examined			Liver Kidneys Portronal far		Thymus Muscle	SM Lymph N Pancreas Trachea	Thyroids Parathyreids Oesophagus	Stomach Duodenum	Jejunum	Colon	Mesenteric LN	Aorta	Adrenals Bronchial LN	Testes	Prostate	Bladder	Mammary Gl	Eyes	Brain	Sternum	Nares	Sciatic nerve	
					utolytic.																			
			y		Apparent depletion of lymphocytes but autolytic.																			
Death	FD		Histopathology		lymphocy																			
De			Histo	tic.	tion of	All sections autolytic.																		
Time on Study	14			Section autolytic.	nt deple	ctions a		tic																
Time				Sectio	Appare	All se	NAD.	Autolytic											•					
>			Sample		s and n	Stomach and Intestines	Mesenteric Lymph Node	Bladder and Eyes																
30 mg HMX/kg/day			?S	Liver	Thymus Spleen	Stoma Intes	Mesen Lymph	Bladd Eyes				-			<u>.</u>									 =
30 mg HB											le.													
Group: 4	6		ory						lings	w fluid.	ry friab													
Gre	Sex:		Clinical History						Necropsy Findings	th yello	odes ve													
416877	7.8		Clini						Necro	lled wit	lymph r													
Project No: 416877	Animal No:			٥.						Abdomen filled with yellow fluid.	Mesenteric lymph nodes very friable.													
Pro	ş			NAD.						₹	æ													 _

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	Number of Sections Examinad			<u>.</u>	Kidorys Porizonal fa		•		21.5	Musele Collection Co	OM Lymph N	Pancreas	hea	Thuronds	Parathyre1ds	Oesophagus	ach	Dyodenum	E	E C	Ę,	c	En	Mesenteric LN	e	Adrenals	Pronchial LN	es	tate	Pitultary	der	SKID Repperie	31 V	,	c '	Spinal cord	E C	Nates Sciatic nerve	341311		
	Sect			1.3 v.·r	Fidneys Periton	1,1117	Heart	Te Jour	Th;mus	01.350E	Σ.	Panc	Trachea	Thur	PAYA	Ç.	Stomach	Dote	11cum	Jejunum	Caecum	Colon	Rectum	Mesc	Anrta	Adre	Pron	Testes	Prostate	Pitu	Bladder	SK1D	1010	Eyes	Brain	Spire.	Sternum	NATES COLDI			
		7	9.9	١																																					
ے			Histopathology																																						
Death	Ŧ.		stopa																																						
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t udy			:																																						
Time on Study	14																																								
Time					NAD.																																				
	,	_																																							
>-			Sample																																						
30 mg HMX/kg/day			S																								•	•													
HMX/				<u> </u>	=	=		=	=	_	=	_	==		-	=	_	=	Ī		=	=		_		=	-	_	=	_	_	=	_	_	=	_			_	-	╡
30 mg																																									
4	ъ																																								
Group:	Sex: C	İ	tory															Necropsy Findings	ĺ																						Ì
Ö	Š		1 H1s															y Fin																							Í
7.71			Clinical History															crops																							
4168	79		เว															Z																							
t No:	 0																																								
Project No: 416877	Animal No:				NAD.															NAD.																					
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Project No: 4187// Croup: 4 30 mg HPD	30 mg HMX/kg/day	Time on Study	Death			
	F== (6:: /::				No. of the last	ĺ
Animal No: 80 Sex: Of		14	T.K		Sections Examined	ned
						HE
Clinical History	Sample		Histopathology			
					Liver	1
NAD.		NAD.			Kidneys Portronal fat	1
					Lunds	
					Heart	口
				-	Spleen	
					Thymus	コ
					Muscle	1
					Salivary Gl	<u>1</u> :
					N Light I W.	1
					Fancteas	1
					Thyroids	1
					Parathyreids	13
					Oescophagus	1
	-				Stomach	1
Necropsy Findings					Duodenum	1
					Ileum	1
CAN					Je junum	1
					Caecum	1:
					Coton	1
	_				Monophonia IN	1
•					Aorta	1
					Adrenals	<u>'</u>
					Bronchial LN	Ц
•	•				Testes	ك
					Prostate	
					Pituitary	ユ
					Bladder	1
					Skin	1
					Mammary Gl	4
					Eyes	4
					Brain	7
					Spinal cord	4
					Sternum	1:
					Cotat to nomin	<u>-ŀ</u>
					יירופניני ייבואני	_
						1
						1

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	Number of	돢			Liver	Kidneys	in in in in in in in in in in in in in i	Trands	neart 2 .	Spiren	Thymus	Saltvary Gl	SM Lymph N	Pancreas	Traches	Thyroids	Para: hyroids	Ocsophagus	Stomach	Duodenum	I letm	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals Bronchial LN	Testes	Prostate	Pituitary	Bladder	Skin	Mammary GI	Eyes	Brain Criss cord	יייין מווייין	Sternum	Nares	Sciatic nerve			1
				37																																							
Death		Ţĸ		Histopathology																																							
Time on Study	(Weeks)	14																																									
	:/kg/day			Sample																									•							~							
	Project No: 416877 Group: 5 75 mg HMX/kg/day	Sex: O		Clinical History			NAD.													Neuropsy Findings	shumur (sedoman		NAD.																				

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	Number of Sections Examined			Liver kidneys	Perfrenal fat	Lunds	Spleen	Thymus	Muscle	SM Lymph N	Pancreas	Trachea	Thyroids	Parathyreids	Oesophagus	Prodenim	Ileum	Jejunum	Caecum	Colon	Mectum	Mesenteric LN	Advonale	Bronchial LN	Testes	Prostate	Pituitary	Bladder	Skin	Free Free	Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
			уу																																	
Death	ТK		Histopathology																																	
Time on Study	14			Foct necrosis.																																
X/kg/day			Sample	Liver																					•											
Project No: 416877 Group: 5 75 mg HMX/kg/day	Animal No: 82 Sex: đ		Clinical History	NAD.												Necropsy Findings		NAD.																		

Project No: 416877 Group: 5 75 mg HMX/kg/day	IX/kg/day	Time on Study	Death	[
Sex: O		7			Number of	•
		14	TK	<u> </u>	Sections Examined	일보
Clinical History	Sample		Histopathology			
					Liver	7
NAD.	Brain	Mid line cyst	Mid line cyst in cerebrum containing cell debris and necrotic material		Perirenal far	19
		Dan ping at tags	ייים רבן זמן.		Lungs	1
				= L	Heart	1
					Thymns	1-
				· Σ	Muscle	H
				<i>v.</i>	Salivary Gl	+
				C.	SM Lymph N	\exists
				<u>~</u>	Pancreas	1
					Trachea	1
				<u> </u>	Thyroids	4
				<u>. (</u>	Parachyreids	Ŀ
				<u> </u>	Oesophagus Stomach	1-
Necrossis Biodicase					Disorberim	Ŀ
chirples dedoctory				-	Ileum	1
				2	Jejunum	-
NAD.				O	Caecum	Ö
				0	Colon	9
·				α	Rectum	\exists
				Σ	Mesenteric LN	<u> 1</u>
				<u>«</u>	Aorta	<u> </u>
				<u> </u>	Adrenals	٠
	•			x .	Bronchial LN	ť
				[- 1	Testes	Ŀ
				<u> </u>	Prostate	ŀ
				<u>.</u> a	Ficulary	Ŀ
				. v.	Skin	Ξ
				I	Mammary Gl	占
				EL .	Eyes	<u> </u>
				<u>a</u>	Brain	<u>ન</u>
				U,	Spinal cord	7
				S	Sternum	_
				Z	Nares	ا
				S	Sciatic nerve	<u>~</u>
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	Number of Sections Examined			Eldneys	Lunds	Heart	Thymus	Musc 10	Calivary Cl	Pancreas	Traches	Thurnids Paral heroids	Supply for the	of only of	Ducdenum	Thoum	Carcium	Colon	Restum	Mesenteric LN	Adronale	Bronchial LN	Testes	Prostate	Pituitary	Skin	Mammary Gl	Eyes	Brain	Spinal cord	Nares	Sciatic nerve	
		7	λ																														
Death	TK		Histopathology																														
Time on Study	14			NAD.																										-			
X/kg/day			Sample																				•										
Project No: 416877 Group: 5 75 mg HMX/kg/day	Sex: O		Clinical History	NAD.											Necropsy Findings		NAD.																

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	N. markon	Sections Examined			Liver	Kidneys Perirenal fat	Lungs	Heart	Հրյասո	Thymus	Salivary Gl	N Hqmyl MS	Pancreas	Trachea	Thyroids	Parathyreids	Stomach	Duodenum	Ileum	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals Propoble 1 1 N	Testes	Prostate	Pituitary	Bladder	Skin	Mammary Gl	Eyes	Brain	Spinal cord	Sternum	Nares	Science nerv		
Death		ЛК		Histopathology																																				
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(/kg/day			Sample		-												-										•										-		
Project No: 416877 Group: 5 75 mg HMX/kg/day	Sex: O		Clinical History		NAD.													Necropsy Findings			NAD.																		

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	Number of	Sections Examined			Liver Kidneys Spleen	Brain																	
Death		Ţĸ		Histopathology																			
Time on Study		14			NAD.				-					-									
200 mg HMX/kg/day	•			Sample				_									•						
416877 Group: 6	Animal No: 101 Sex: of	101		Clinical History	NAD.							Necropsy Findings	NAD.										

	P			Щ	
	Number of Sections Examined		Liver Kidneys Bpleen Brain		
Time on Study Death	FD	Histopathology	Some autolysis, otherwise NAD. Not examined.		
200 mg HMX/kg/dav		Sample	Liver Thymus) Lungs)		•
Project No: 416877 Group: 6 200 mg HJ	Sex: O	Clinical History	NAD.	Necropsy Findings	Liver - very soft and pale with dark red patches. Thymus - enlarged. Lungs - dark red.

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	Number of Sections Examined		1,000	Elan Brain
		7007	Ikar	
Death	TK	utetonetological	our adores	
Time op Study	14			NAD.
200 mg HMX/kg/day		Alcama		•
6 200 mg HM				
Group:	Sex: o	Clinical History		Necropsy Findings
3: 416877	: 103	Clinica		Necrops
Project No: 416877	Animal No:			NAD.

	Γ	Ped	벌		
	Mahor	Sections Examined			Liver Kidneys Kpleen Brain
				,	
Death		FD		Histopathology	
Time on Study	(Curam)	3			NAD but PM change.
200 mg HMX/kg/dav	[mm (6:: /:			Sample	•
Project No: 416877 Group: 6 200 mg HJ		.xux		Clinical History	Necropsy Findings NAD.

	ined	벌		
	Number of Sections Examined			Liver Kidneys Kidneys Brain
t.			Histopathology	
Death	TX		Histop	
Time on Study	14			NAD.
200 mg HMX/kg/day			Sample	•
Project No: 416877 Group: 6 200 mg HA	Animal No: 105 Sex: o		Clinical History	Necropsy Findings NAD.

į	3	뒫		~~ -	\prod	
	Number of			Liver Kidneys Gpleen Brain		
			У	·		
Death	FD		Histopathology			
Time on Study	2			NAD.		
200 mg HMX/kg/day	1		Sample			•
Project No: 416877 Group: 6 200 mg HA	Sex: O		Clinical History	NAD.	Necropsy Findings	NAD.

	lned	보	ľ	
	Number of Sections Examined			Kidncys Kidncys Bpleen Brain
				·
	_]	logy	
Death	FD		Histopathology	
Time on Study	2			
Time of				NAD.
200 mg HMX/kg/day			Sample	•
OO mg HM		Ì		
Group: 6 2	6 5		Clinical History	Necropsy Findings
. 416877	107		Clinica	Necrop
Project No: 416877	Animal No:			NAD.

	fred	보	\coprod	
	Number of Sections Examined			Liver Kidneys Spleen Brain
	T	1	ĄĄ	
Death	FD		Histopathology	
Time on Study	2			NAD.
200 mg HMX/kg/day			Sample	•
Project No: 416877 Group: 6 200 mg H	Sex: O		Clinical History	White exudate under eyelids when found dead. Necropsy Findings NAD.

	ned	보	П	
	Number of Sections Examined			Lidery Kidneys Spleen Brain
			γ	
Death	ТT		Histopathology	
Time on Study	14			NAD.
MX/kg/day			Sample	•
Project No: 416877 Group: 6 200 mg HMX/kg/day Animal No: 109 Sex: Ĉ			Clinical History	Necropsy Findings NAD.

		ned	보		77-7	Ш	П	
		Number of Sections Examined			Liver Kidneys Spleen Brain			
Death		TK		Histopathology				
Time on Study	(WEEKS)	14			NAD.			·
VA /1-0-/-3	wy vg/ day			Sample				•
77 Group		Animal No: 110 Sex: O		Clinical History	NAD.		Necropsy Findings	NAD.

	alned	볓		
	Number of Sections Examined			Liver Kidneys Spleen Brain
				-
<u></u>		,	97	
Death	FD		Histopathology	
Time on Study	9			NAD.
200 mg HMX/kg/day			Sample	. •
200 mg HM		Ī		
Group: 6	Sex: o		Clinical History	Necropsy Findings
416877	111		Clinic	Ne Cr O
Project No: 416877	Animal No:			NAD.

	Tued	보	Ī			
	Number of Sections Examined			Liver Kidneys Bpleen Brain		•
	_					
			У			
Death	TK		Histopathology			
			Hist	· p·		
Time on Study	14			Not examined		
Tim		-	_	ž		
200 mg HMX/kg/day			Sample	Bladder		•
.00 mg HM		Ī				
٠	6		ory		ings	·
Group:	Sex:		Clinical History		Necropsy Findings	ਹੈ. ਹ
: 416877	112		CIID		Necre	Bladder distended.
Project No: 416877	Animal No: 112			ZAD.		Bladder
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	Number of Sections Examined		Liver Kidneys Spleen Brain
			·
	· · · · · ·	yex	
Death	FD	Histopathology	
Time on Study	4		NAD.
200 mg HMX/kg/day		Sample	•
200 mg HM			
Group: 6	Sex: O	Clinical History	Necropsy Findings
Project No: 416877	1 No: 113	Clini	
Proje	Animal No:		NAD.

	Γ	를 보		
	Number of	Sections Examined		Liver Kidneys Bpen Brain
4			Histopathology	
Death	È	I	Histop	
Time on Study	7.			NAD.
200 mg HMX/kg/day	• •		Sample	•
Project No: 416877 Group: 6 200 mg HJ	Sex: O		Clinical History	NAD.

	Γ	Ped	보	\Box	77	[m	\prod	П	П	\prod	П	П	П	П	П	П	П	П	П	Π			Ш
	Number of	Sections Examined			Liver	Brain									<u> </u>		<u>.</u>					,	
				,			•																
Death		FD		Histopathology								•											
Time on Study	,	5			NAD.																•		
200 mg HMX/kg/day				Sample														•					
Project No: 416877 Group: 6 200 mg H	•			Clinical History	NAD.								Necropsy Findings	NAD.									

	al ned	벌	
	Number of Sections Examined		Liver Kidneys Spleen Brain
·		<u>}</u>	
Death	FD	Histopathology	
Time on Study	6		NAD.
1X/kg/day		Sample	•
_	Sex: G	Clinical History	Necropsy Findings
	o: 116	Clinica	Necrops
Project !	Animal No:		NAD.

	ined.		
	Number of Sections Examined		Liver Kidneys Spleen Brain
			·
Death	FO	Histopathology	
Time on Study	1		NAD.
200 mg HMX/kg/day		Sample	•
Project No: 416877 Group: 6 200 mg HJ	Sex: o	Clinical History	NAD. NAD.

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보		Liver Kidneys Spleen Brain	·
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	Histopathology		
		NAD.	·
	Sample		•
	Clinical History	NAD.	NAD.
		Sample Histopathology	Clinical History Sample Histopathology NAD.

	ſ	ned	핖			
		Number of Sections Examined			Liver Kidneys Spleen Brain	
Death		FD		Histopathology		
Time on Study	(Weeks)	8			Not examined.	·
200 ms vav. 24. 24.	un/kg/aay			Sample	Skin, penus, preputial glands, thigh muscle and thymus	•
Project No: 416877 Group: 6 200 mg u				Clinical History	NAD. Necropsy Findings Skin - bald patches. Penis - excreted bright yellow	material. Preputial glands enlarged. Right leg thigh muscle - friable. Thymus enlarged.

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	Number of	2		_	Kidneys Perirenal fat	v		e.	r. c	Salivary Gl	CM Lyminh N	reas	6 90	olds	raratnyroids	Orsophanus Stomach	E COL		mur.	Ę	ا ج	Ę	Mesenteric LN		Bronchial LN	5	Sec	s.	Pituitary	der		Mammary Gl	_	Spinal cord	Ē		Sciatic nerve	
	2 400			Liver	Kidneys Periren	Lungs	Heart	roold:	Thymus Musch	3.15	بر ج	Pancreas	Trachea	Thyroids		or sornar	Ducdenin	Ileum	Jejunum	Caecum	Colon	MO C C C	Mesen	Adress	Bron	Ovaries	F tubes	Uterus	Pitu	Bladder	Skin	Maria	Eyes	Spine	Sternum	Nares	Scia	
			İ																																			
			Histopathology																																			
Death		ا	path																																			
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Time on Study																																						
Week	7	-			Ö.																																	
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Group:	Sex:		Histo	ļ													1 2 4 4																					
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16877	=		Clinical History														Necrones Etadings																					
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it No	No:				NAD.														2																			
Project No: 416877	Animal No:		-		N														2	ž																		
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	Number of	Sections Examined			LIVOF	Kidneys	1.	Lunds	Heart	Spleen	Thymus	Muscle	Salivary Gl	N think I W.	Pancreas	Trachea	Thyroids	Parathyro'ds	Oesophagus	Stomach	Ducylennam	Ileum	Je junum	Carcum	Colon	Rectum	Mescnteric LN	Aorta	Adrenals	Bronchial LN	Ovaries	F tubes	Uterus	runtary	Bladder	Skin	Mammary Gl	Eyes		Spindi cord	Sternum	000000	ייין מרזר וובדאב	
				γ																																								
Death	¥	41		Histopathology																																								
Time on Study	1.4					NAD.																																						
		-		Sample																										•														
	122 Sex: 9			Clinical History																	Necropsy Findings																							
Project No:	Animal No:				-	NAD.												_			_		CAM	-														_						

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	Number of Sections Examined			Liver Kidneys Perirenal fat	Lungs Heart	Spicen	Thymus Muscle	Salivary Gl	SM Lymph N Pancreas	Trachea	Thyroids Parathyroids	Oesophagus	Stomach	Duodenum Ileum	Jejunum	Caecum	Colon	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Varies F rubes	Uterus	Pituitary	Bladder	Skin	Mammary Gl	Eyes Brain	Spinal cord	Sternum	Nares	sciatic nerve	
			y																														
Death	TK		Histopathology		caining cells.																												
Time on Study	14			Cystic glands.	Focus brown staining cells.																												
			Sample	Uterus	Ovaries												_			•													
Project No: 116877 Group: 1 Control	123		Clinical History	NAD.										Necropsy Findings	Can																		

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	Number of Sections Examined			Liver Kidneys	Perirenal fat	Lunds	Spleen	Thymus	Muscle	OM Lymph N	Pancreas	Traches	Thyroids	Opsorbagus	Stomach	Duodenum	Ileum	Jejunum	Caecum	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	F tubes	Uterus	Pituitary	Bladder	Managary Gl	Eyes	Brain	Spinal cord	Nares	Sciatic nerve		
Death	TK		Histopathology	h. neohable above	Area polymorphs, probably abcess.																															
Time on Study	14				Area polymorp																															
			Sample		Muscre																		•	•												
416877 Group: 1 Control			Clinical History													Necropsy Findings																				
Project No: 416877	Animal No:	1			NAD.							_						-	NAD.				-													

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	Number of Sections Examined			niver Kidneys	Perirenal fat	Lunds	Spleen	Thyras	Muser]c	SM Lymrds N	Pancreas	Traches	Thyreids Parathyreids	Oesophagus	Stomach	Duodenum	Jeyunum	Caecum	Colon	Rectum Mesonterio 10	Aorta	Adrenals	Bronchial LN	(waries	r tubes	Pituitary	Bladder	Skin	Mammary Gl	Eyes Brain	Spinal cord	Sternum	Hares	Sciatic nerve	
		,																																	
Death	TK		Histopathology																																
Time on Study	14			Q Z	.000																														
			Sample																		-		•												
416877 Group:	125 Sex: Q		Clinical History													Necropsy Findings																			
Project No:	Animal No:			CAN														NAD.	_			•													

Project No: 116877 Group: 1 Control		Time on Study	Death			
					Mumber	ĺ
Animal No: 126 Sex: V		14	TK		Sections Examined	ned
						HE
Clinical History	Sample		Histopathology	,		
					Liver	<u> 1</u>
NAD.		NAD.			Eldneys Perironal fat	<u> </u>
					Lungs	Ľ
					Heart	너
					Spleen	ᆸ
					Thymus	\exists
					Muscle	1
					Salivary Gl	₫
					N Homer N	2
					Pancreas	1
					Trachea	1
					Thyroids	1
					Parathyroids	1
					Oesophagus	4
					Stomach	4
Necropsy Findings					Duodenum	4
					Ileum	4
					Jejunum	4
NAD.					Caecum	4
					Colon	L
					Rectum	\vdash
					Mesenteric LN	4
					Aorta	4
					Adrenals	4
	•				Bronchial LN	4
					Ovaries	4
					F tubes	4
					Uterus	4
					Pituitary	4
					Bladder	1
					Skin	=
					Mammary Gl	9
					Eyes	۲.
					Brain	_
					Spinal cord	Ċ.
					Sternum	4=
					Nares	0
					Scintic nerve	Ŀ
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	Number of	Sections Examined		1000	Kidneys	Perirenal fat	Lungs	Spiren	Thymus	Muscle Salivary Gl	N HOMEN NO	Pancreas	Trachea	Parathyroids	Oesophagus	Stomach	Ducdenum	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Adrenale	Bronchial LN	Ovaries	F tubes	Uterus	ricultary	Bladder	SKID	Fyes	Brain	Spinal cord	Sternum	Naros	Sciatic nerve	
				Y																													-				
Death		TK		Histopathology																																	
Time on Study		14			NAD.																																
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Control			ſ													Ī	Ī																_			_	
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Group:				HISTO												26.24																					
416877	127	171	1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Ciinicai History												No rough	weeropsy randangs																				
Project No:	Antmal No.	· ON 181117			NAD.														NAD.												-			-1: -i-			

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	Number of Sections Examined			Liver	Perirenal fat	Lunds	Heart	יייוןלי	Thymus	Salivary Gl	SM Lymph N	Pancreas	Trachea	Ingresids Parathyroids	Oesophagus	Stomach	Duodenum	Ileum	Jejunum	Caecum	Colon	Merchan	Anta	Adrenals	Bronchial LN	Ovaries	F tubes	Oterus	ricuitally Disdan	Skin	Mammary Gl	Eyes	Spinal cord	Sternum	Criatic nerve	343	
			y.																																		
Death	TK		Histopathology		Focus fat cells in ventricle.																																
Time on Study	14				Focus fat ce																																
			Sample		Brain																				•												
416877 Group:	128 Sex: 9		Clinical History														Necropsy Findings																				
Project No:	Animal No:			2	NAD.		-												CAN																	-	

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	Number of	Sections Examin		Liver Kidneys Derivenal fat	Lunge	Heart Crieen	Thyrus	Salivary Gl	SM Lymph N Pancreas	Trachea	Ingredus Parathyroids	Oesophagus Stomach	Duodenum	Ileum	Jejunum	Caecum	Rectum	Mesenteric LN	Aorta	Bronchial LN	Ovaries	F tubes	Oterus Pituitary	Bladder	Skin	Mammary Gl	Eyes Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
			1y																													
Death	TK		Histopathology																													
Time on Study	14			NAD.																												
			Sample															-		•				-								
Project No: 416877 Group: 1 Control	129		Clinical History	NAD.									Necropsy Findings		CAX																	

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	Number of Sections Examined			Kidneys	Perirenal fat	Heart	Spicen	Muscle	Salivary Gl	Pancreas	Trachea	Thyroids	Parathyroids	OPSOpnagus Stomach	Duodenum	Ileum	Jejunum	Caecum	Rentum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Ovaries	r tubes	Pituitary	Bladder	Skin	Manmary Gl	Eyes	Spinal cord	Sternum	Nares	Sciatic nerve	
			,																																
Death	ТK		Histopathology																																
Time on Study	14			NAD.									-																						
	•		Sample			_																•													
Control		Ì														Ī					-														
S T																																			
Group :			Clinical History												Necropsy Findings																				
416877			Clinica												Necrops																				
Project No:	Animal No:			NAD.													NAD																		

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	Number of Sections Examined			Fidneys Perirenal fat	Lunge	Selven Tymus	Muscle Salivary Gl	CM Lymph N Panereas	Trachea Thyroids	Parathyroids	Oesophagus Stomach	Duc-Irnum	Jejunum	Colon	Rectum Mescuteric LN	Acrts	L'N	Ovaries F tubes	Uterus	Fituitary	Skin	"ammary Gl	Eyes Brain	Spinal cord	Sternum	Sciatic nerve		
		_	, A1																									
Death	FD		Histopathology	ytic.																								
Time on Study	11			Tissues autolytic.	Congested.									_														
			Sample		Lungs	·											•											
Project No: 416877 Group: 1 Control	Animal No: 131 Sex: 9		Clinical History	Found dead after being trapped in food								Necropsy Findings	Animal in state of autolysis.	Very lean, little body fat available.	Constibated.		Lungs reader than normal.											

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	Number of	Sections Examined			Liver	Friends Perfeenal fat	Lungs	Heart	Spicen	Thymus	Salivary Gl	SM Lymph N	Pancreas	Trachea	Thyroids	Parathyroids	Oesophagus	Stomach	Duodenum	I leum	Je junum	Caecum	Postin	Monombouto IN	Anria	Adrenale	Bronchial LN	Ovaries	F tubes	Uterus	Pituitary	Bladder	Skin	Mammary G1	Brain	Spinal cord	Sternum	Nares	Schatle nerve	
				γγ																																				
Death		TK		Histopathology																																				
Time on Study		14				NAD.																																		
				Sample																							•													
Project No: 416877 Group: 1 Control	132 500. 0	132 SEX:		Clinical History		NAD.													Necropsy Findings															==						

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	Number of	THE CASE OF THE PARTY OF THE PA		L.1 Vr. F	Perfirenal fat	Lungs	Beart	Thymus	Muscle	Salivary G	Pancreas	Trachea	Thyroids Parathuro'ds	Cocophague	Stomach	Ducrtenum	11.cm	Jejunum	Caecum	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	(Waries	Uterus	Pituitary	Bladder	Skin	Mammary G1	Brain	Spinal cord	Sternum	Sciatic nerve	
		_	,																																
Death	ŢK		Histopathology																																
Time on Study	14				NAD.							_																							
	•	_	Sample			-																		•											
416877 Group:	: 133 Sex: 9		Clinical History										- 5			Necropsy Findings																			
Project No:	Animal No:				NAD.													NAD.																	

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No: 416877 Group: 1 Control	134 Sex: Q		Clinical History													Necropsy Findings																			
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	Number of	Sections Examined		Liver Kidneys Syleen Brain
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Death	F F	¥	Histopathology	
Time on Study	14			NAD.
/kg/dav			Sample	•
Project No: 416877 Group: 2 10 mg HMX/kg/day	141 Sex: 9		Clinical History	NAD.

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Death	TX		Histopathology	
Time on Study	14			NAD.
/kg/day	•		Sample	•
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	Number of			Liver Kidneys	Spleen																 		
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Death	ТX		Histopathology																				
Time on Study	14			CAN											_								
/kg/day			Sample														•						
. 416877	Animal No: 143 Sex: 9		Clinical History	NAD.									Necropsy Findings	NAD.									

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	Number of Sections Examined			Liver Kidneys Spleen Brain
			y	lning
Death	TK		Histopathology	Cerebrum - 2 mid line cysts lined by stratified squamous epithelium, one containing keratin-like material, one contaicell debris and necrotic material.
Time on Study	14			Cerebrum - 2 m. stratified squtaining keratioell debris and
/kg/day	•		Sample	Brain
Project No: 416877 Group: 2 10 mg HMX/kg/day	144 Sex: 9		Clinical History	NAD.

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Project No: 416877 Group: 2 10 mg HMX/kg/day	Sex: 9	Clinical History	Necropsy Findings
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Death		Histopathology	
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Time on Study	14		NAD.
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Project No: 416877 Group: 2 10 mg HMX/kg/day	147 Sex: Q	Clinical History	
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	148 Sex:		Clinical History									Necropsy Findings									
Project No:	Animal No:			NAD.									NAD.								

416877 Group: 2 10 mg HMX/kg/day	kg/day	Time on Study	Death	Number of
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	Number of Sections Examined		Midneys Spleen Brain
Death	TK	Histopathology	
Time on Study	14		NAD.
/kg/day		Sample	•
16877 Group: 2 10 mg HMX/kg/day	150 Sex: Q	Clinical History	Necropsy Findings
Project No: 416877	Animal No: 15		NAD.

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	Number of Sections Examined			Liver	Spleen Brain											_			·	 		
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Death	TK		Histopathology																			
Time on Study	14			NAD.																		
/kg/day			Sample										-				•					
777	Sex:		Clinical History									Necropsy Findings										
Project No: 416	Animal No: 151		U	NAD.								Ne		NAD.								

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	Number of Sections Examined			Kidneys Spleen Brain										
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Death	ТX		Histopathology											
Time on Study	14			NAD.										
/kg/dav	7		Sample							•	 			
Project No: 416877 Group: 2 10 mg HMX /kg/dav	152 Sex: 9		Clinical History	Tip of tail missing throughout study.				Necropsy Findings	NAD.					

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	Number of Sections Examined			Livey Kidneys Spieen Brain
Death	TK		Histopathology	
Time on Study	14			NAD.
/kg/day			Sample	•
p: 2 10 mg HMX/kg/day			יץ	19.5
416877 Group:	153 Sex:		Clinical History	Necropsy Findings
Project No: 416877	Animal No:			NAD.

	g g	벌	
	Number of Sections Examined		Liver Spleen Brain
		X	·
Death	TK	Histopathology	
Time on Study	14		NAD.
/kg/dav		Sample	•
Project No: 416877 Group: 2 10 mg HMX/kg/dav	154 Sex: 9	Clinical History	Necropsy Findings . NAD.

	P	벞	F	
	Number of Sections Examined			Brain Brain
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Death	TK		Histopathology	
Time on Study	14			NAD.
/kg/day			Sample	•
Project No: 416877 Group: 2 10 mg HMX/kg/day	155 Sex: Q		Clinical History	NAD.

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1	Number of	Sections Examined		Liver Kidneys Spleen Brain					
Death	14.6	,	Histopathology						
Time on Study	14	;		NAD.	-				
/kg/day	1		Sample						•
Project No: 416877 Group: 2 10 mg HMX/kg/day	Sex: 9		Clinical History	NAD.				Necropsy Findings	NAD.
Projec	Animal			NAD	. . <u>.</u>				NAD

	Γ	P d		
	Number of	Sections Examined		Kidheys Spleen Brain
Death	È	T.K	Histopathology	
Time on Study		14		NAD.
/kg/dav			Sample	•
Project No: 416877 Group: 2 10 mg HMX/kg/day	Sex: 9		Clinical History	Necropsy Findings NAD.

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	Number of Sections Examined			Liver Kidneys Spleen Brain	17 8 7 C											 	
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Death	TK		Histopathology														
Time on Study	14			NAD.				_									
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o: 416877 Group: 2 10 mg HMX/kg/day	158 Sex:		Clinical History						Necropsy Findings		-						
Project No:	Animal No:			NAD.						NAD.					· · · -		

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	Number of Sections Examined		Liver Kidneys	Brain								·	 			-	
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Project No: 416877	Animal No:		NAD.							NAD.							
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Number o Sections Exa		Fidneys Spleen Brain
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TK	Histopatho	
14		NAD.
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Animal No: 160 Sex: 9	Clinical History	NAD. NAD.
	160 Sex: 9 Sections Examin	160 Sex: 9 Clinical History Sample Histopathology

Project No. 11677 Group: 3 30 mg HMX/kg/day Time_Golgstudy Death TIX Sections Enablined Multiple of call missing from week 6. 14	Į		P	불	\perp	٦,	4.4	\sim	4	1	1-	占	4	4	<u> </u>	40	<u>1</u> -	Ŀ	Н	4	႕	4	4	4	4	4	7-	?	4	4	4	<u> </u>	- -	2	~	~	_		0	Ŀ
161 Sex: Q Time on Study 161 Sex: Q 148 Clinical History Sample tail missing from week 6. Necropsy Findings		Number of	Sections Exami			Librare	Perirenal fat	Lungs	Heart	Spleen	Thyras	Salivary Gl	N damyl M	Pancreas	Trachea	Thyroids Parathyroids	Orsorhagus	Stomach	Duodenum	[]eum	Je junum	Caecum	Colon	Rectum	Mescnteric LN	Aorta	Acrenals Bronchial IN	Ovaries	F tubes	Uterus	Pituitary	Bladder	Skin	Eves	Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
161 Sex: Q Time on Study Clinical History Lail missing from week 6. NAD.					Å																																			
161 Sex: 9 Clinical History Clinical History Clinical History Acropsy Findings Necropsy Findings	Death		ТХ		Histopatholog																																			
161 Sex: 9 Clinical History tail missing from week 6. Necropsy Findings	Time on Study		14				NAD.																																	
clinical History tail missing from week 6 Necropsy Findings	IX/kg/day	-			Sample																							•												
	416877 Group: 3		161		Clinical History		Tip of tail missing from week 6.												Necropsy Findings			MAD.																		

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Project No: 416877	Animal No:				NAD.													NAD.																		
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Histopathology Liver Kidneys Cidneys	
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Liver Kidneys Perirenal fatt Lungs Heart Spleen Thyrus Musele Salivary Gl Salivary Gl Salivary Gl Musele Salivary Gl Parathyreids Parathyreids Parathyreids Parathyreids Pereum Lleum Lleum Lleum Lleum Colon Rectum Rectum Rectum Mesenteric LN Acrta Acrta Adrenals Pituitary Ridder Skin Mammary Gl Eyes Brain Spinal cord Sternum Nares	
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Clinical History Sample NAD. Histopathology Liver Fridneys Fr	164 Sex: Q		14	TK		Number of	3
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Necropsy Findings	Clinical History	Sample		Histopatholog	^		
Necropsy Findings .						Liver	<u> </u>
Necropsy Findings	NAD.		NAD.			Kidneys Perirenal fat	~ -
Necropsy Findings						Lungs	7
Necropsy Findings						Heart	1
Necropsy Findings						Spleen	1
Necropsy Findings						Thymus	1-
Necropsy Findings						Salivary Gl	1-
Necropsy Findings						N thimpy N	Ц
Necropsy Findings						Pancreas	ı
Necropsy Findings						Trachea	9
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						Jejunum	Ц
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			-			Colon	_
						Rectum	1
						Mesenteric LN	<u> 1</u>
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Death	TK		Histopathology		tes.																																	
Time on Study	14				Foci lymphocytes.																																	
X/kg/day			Sample		Liver																					-	•											
416877	Animal No: 165 Sex: 9		Clinical History		NAD.													Necropsy Findings		NAD.																		

	30 mg HMX/kg/day	Time on Study	Death	•		
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Clinical History	Sample		Histopathology			Ш
					Liver	<u>1</u> 2
NAD.	Spinal Cord	Laminated cyst.			Perirenal fat	口
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					Thyroids	7
					Parathyroids	4
					Oesophadus	4
					Stemach	1
Necropsy Findings					Duodenum	1
					Ileum	4
Cen	-				Jejanum	1
NAD.					Caecum	4
					Colon	4
					Rectum	
					Mesenteric LN	<u>d</u>
					Aorta	4
					Adrenals	1
	•				Bronchial LN	4
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					Uterus	4
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					Eyes	7
					Spinal cord	٧-
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Gro	Sex:		Clinical History	cage 11											sy Find		r and r	h clot																	
416877	168		Clinica	Head crushed by cage lid.											Necropsy Findings		nt ane	ed wit																	
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Number of	Sections Examined			Perirenal fat	Lungs	Heart	Spleen	Thymus	Muscle 651 (1937)	SM Lymph N	Pancreas	Trachea	Thyroids	rarathyro, ds	Oesophagus	Description	J.eum	Jejunum	Carcum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Ovaries	sagn .	Pituitary	Bladder	Skin	Mammary Gl	Eyes	Crimal cond	Spanar cord	Scietic nerve		
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Project No: 416877 Group: 3 30 mg HMX/kg/day Animal No: 171 Sex: Q	Clinical History	NAD.								Necropsy Findings	Can																

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	Number of Sections Examined			Liver Kidneys	Perirenal fat	Lungs	Spiecn	Thymus	Muscle Salivary Gl	SM Lymph N	Pancreas	Trachea Thyreids	Parathyroids	Oesophaqus	Stomach	Ductenum	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Recorded to	Ovaries	F tubes	Uterus	Pituitary	Bladder	Skin	Mammary Gl	Eyes Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
Death	TK		Histopathology																																	
Time on Study	14			CAN																																
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Project No: 416877 Group: 3 30 mg HMX/kg/day	173 Sex: 9		Clinical History	ZAD.												Necropsy Findings		NAD.																		

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Number of Sections Examined			Kidneys	Perirenal fat	Lungs	Spicen	Thymus	Muscle	Salivary GI SM Lymph N	Pancreas	Traches	Inyroids Parathyroids	Oesophagus	Duodenum	Ileum	Jejunum	Caecum	Rectum	Mesenteric LN	Aorta	Adrenals Brouchtal IN	Ovaries	F tubes	('terus Dienie	Bladder	Skin	Mammary Gl	Eyes Brain	Spinal cord	Sternum	Sciatic nerve		
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X/kg/day		Sample																			_	•											
Project No: 416877 Group: 3 30 mg HMX/kg/day Animal No: 374 Sex: Q		Clinical History		NAU.										Necrosey Pindings		NAD.																	

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	Number of	Sections Examined			Liver	ridneys Perirenal fat	Lungs	Heart	fpleen	Thymus	Muscle	Salivary Gl	Pancreas	Trachea	Thyroids	Parathyroid,	Oesophagus	Stomach	Duodenum	I leum	Jejunum	Caecum	Colon	wac r nm	Mesenteric LN	Adressie	Rronchial IN	Ovaries	F tubes	Uterus	Fituitary	Bladder	Skin	Mammary G1	Eyes Brain	Spinal cord	Sternum	dares	Sciatic nerve		
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Group:		176 Sex: ¥		Clinical History															Necropsy Findings																						
Project No: 416877		Animal No:				NAD.															NAD.																				

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	Number of	Sections Examined			Liver	Vidneys	Tot Inchitable	Sound	Heart	Spleen	Thyras	40.25.16	N CAMPAINS	Pancreas	Trachea	Thyroids	Parathyroids	Oesophagus	Stemach	Duodenum	munut 91.	million C	Colon	Rectum	Mesenteric LN	Aorta	Adrenals	Bronchial LN	Ovaries	Lunes	Pituitary	Bladder	Skin	Mammary Gl	Eyes	DIGINI CLINE	nios reutdo	Navos	Colatic nerve		
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Death	i	TK		Histopathology																																					
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416877 Group:	178 Sex: Q			Clinical History																Necropsy Findings																					
Project No:	Animal No:					NAD.															-	QW							-												

Project No: 416877 Group: 3 30 mg HMX/kg/dav	//kg/dav	Time on Study	Death			
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Animal No: 179 Sex: V	·	14	TK	S.	Sections Examined	2
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Clinical History	Sample		Histopathology			
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~~~				G.	Salivary Gl	<u> </u>
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	Number of	DECLIOUS EXAMIN			ridnevs	Perfrend for	Lunds	Heart	Spieen	Thymus	MUSC16	CM Lymph N	Pancreas	Trachea	Thyroids	Parathyroids	Oesophaqus	Stomach	Duodenum	TI PUB	Jejunum	Caecum	Porting Porting	Mocontorio	Anria	Adrenale	Bronchial LN	Ovaries	F tubes	Uterus	Pituitary	Bladder	Skin	Mammary Sl	Eyes	Spinal cord	Sternum	Hares	Sciatic nerve		
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Death	ΤK			Histopathology																																					
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x/kg/day				Sample								_								_								•													
Project No: 416877 Group: 3 30 mg HMX/kg/day	Sex: 0			Clinical History		NAD.													Necropsy Findings		NAD.																				

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Number of Sections Examined			Kidneys	Perironal fat	Lungs	Spicen	Thymus		Salivary GI	Pancreas	Trachea	Thyroids	Parathyroids	Gresophagus Stemach	Ducdenum	11eum	Je junum	Caecum	Colon	Ment um	Anta	Adrenals	Bronchial LN	Ovaries	F tubes	Oterus	Bladder	Skin	Mammary Gl	Eyes	Cain rord	Sternie	Nares	Sciatic nerve	
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mal No: 181 Sex: Q		Clinical History	CAN												Necropsy Findings			NAD.																	
	Sex: \$ TK	181 Sex: 9	181 Sex: V TK Clinical History Sample Histopathology	181 Sex: 9 Clinical History Sample Histopathology	181 Sex: 9 Clinical History Sample NAD.	181 Sex: 9 Clinical History Sample NAD.	Clinical History Sample NAD.	Clinical History Sample NAD.	Clinical History Sample NAD.	Clinical History Sample Histopathology NAD.	Clinical History Sample Histopathology NAD.	Clinical History Sample Histopathology NAD.	Clinical History Sample Histopathology NAD.	Clinical History Sample Histopathology NAD.	Clinical History Sample Histopathology NAD.	Clinical History  Clinical History  Sample  NAD.  NAD.	Clinical History  Clinical History  NAD.  Necropsy Findings	Clinical History Sample Histopathology  Clinical History NAD.  NAD.	Clinical History Sample Histopathology NAD. NAD.	Clinical History Sample Histopathology  NAD.  NAD.	Clinical History Sample Histopathology NAD.  NAD.	Clinical History Sample Histopathology  NAD.	Clinical History Sample Histopathology NAD.  NAD.	Clinical History Sample Histopathology NAD.	Clinical History Sample Histopathology NAD.	14   TK     TK	Clinical History Sample Histopathology  Necropsy Findings  .	Clinical History Sample Histopathology Necropsy Findings  .	191   Sex: 9	191   Sex: 9	14   TK	14   TK	Clinical History Sample Histopathology  Necropsy Findings  .	Clinical History  Clinical History  NAD.  NAD.	Clinical History Sample Histopathology Necropsy Findings  .

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Number of Sections Examined		Liver	Lunds Lands	Beart	(jeloon	Thymus	Salivary Gl	CM Lymph N	Pancreas	Thyroids	Parathyro'ds	Oescphagus	Stoffach	11eum	Jejunum	Caecum	Colon	Mesenteric LN	Aorta	Adrenals	Pronchial LN	Ovaries F tubes	Uterus	Pituitary	Bladder	Skin	Mammary G1	Eyes Brain	Spinal cord	Sternum	Mares	פכזפרזכ וובו אב	
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Death	Histopathology	cyst containing laminated																															
Time on Study		Sub-meningeal	material.																														
X/kg/day	Sample	Brain																			•												
Project No: 416877 Group: 4 90 mg HMX/kg/day Animal No: 182 Sex: 💡	Clinical History	NAD.												necropsy rundings	4 ::	NAD.																	

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Number of Sections Examined		Liver	Kidneys	Perirenal fat	Lungs	Heart	Spleen	Thymus	Salivary Gl	SM Lymph N	Pancreas	Trachea	Thyroids	Coronbania	Offsophagus Stomach	Duodenum	Ileum	Jejunum	Caecum	Colon	Kectum Moscotoria IN	Mesenteric La	Adrenals	Bronchial LN	Ovaries	F tubes	Uterus	Pituitary	Bladder	Skin	Mammary G1	tyes Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
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X/kg/day	oleme 2	ardinec																						•													
Project No: 416877         Group: 4 90 mg HMX/kg/day           Animal No: 183         Sex: Q	1 ( c ) ( c )	CIONETH HEALTH		NAD.												Necropsy Findings		NAD.																			

Time_weeks; budy Death  If TK Sections Examined HE Histopathology Liver Chlorys Professional Fat Chlorys Professional Fat Chlorys Professional Fat Chlorys Professional Fat Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Chlorys Ch
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90 mg HMX/kg/day
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Group: Sex: History Finding
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184 Sex: Clinical History Necropsy Findings
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		14	TK	Number of Sections Examined
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Clinical History S	Sample	H1s	Histopathology	
	יסאקיים	Slight congestion	slight congestion in lamina propria.	Kidneys Portrenal fat
•				Lungs
				Heart
<u> </u>				Thymus
				Muscle Calivary Gl
				SM Lymph N
-				Pancreas
				Trachea
•				Thyroids Darathyroide
				Describanis
				stomach
Necroses Pladings				Duodenum
				Ileum
-				Jejunum
				Caecum
				Perfu
				Mesenteric LN
				Aorta
				Adrenals
				Bronchial LN
	•			Ovaries
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				Brain
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				Sciatic nerve

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	Number of Sections Examined			Liver	Perfrenal fat	Lungs	Heart	Splern	Thymus	Muscle Salivary Gl	SM Lymph N	Pancreas	Trachea	Thyroids	Parathyroids	Oesophagus	Duodenim	Ileum	Jejunum	Caecum	Colon	Meetium Meetintorio	Aorta	Adrenals	Bronchial LN	Ovaries	F tubes	orerus Pituitary	Bladder	Skin	Mammary Gl	Eyes Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
Death	TK		Histopathology																																		
Time on Study	14				NAD.										_																						-
X/kg/day			Sample																						•												
Project No: 416877 Group: 4 90 mg HMX/kg/day	Animal No: 186 Sex: 9		Clinical History		NAD.												Necropsy Flad tage	chirples Indospe		NAD.																	

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	Number of	Sections Examined			Liver	Kidneys	Tribate Inc.	Lungs	Heart	יייייייי	Thymus	Muscle	Salivary Ci	Pancreas	Trachea	Thyroids	Parathyroids	Oesophagus	Stomach	Duodenum	1 leum	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals propoble 1	Stonental La	F tubes	Uterus	Pituitary	Bladder	Skin	Mammary Gl	Eyes	Spins) cord	Division Core	Sterner Sterner	Cotation perve	ארזור וופואפ	
Time on Study Death		14 TK		Histopathology		NAD.																																				
<b>L</b>	L_	]		Sample								_						_		-									•				-				_					
Project No: 416877 Group: 4 90 mg HMX/kg/day	0	10/ SEA:		Clinical History		NAD.														Necropsy Findings		NAD.																				

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	Number of	Sections Examined			Liver	Perfrenal fat	Lungs	Heart	Spicen minimum	Muscle	Salivary Gl	SM Lyminh N	Pancreas	Trachea	Thyroids	Parathyroids	Oesophagus	Stomach	Duodenum	I leum	Jejunum	Caecum	Colon	Kectum	Mesenteric LN	Aorta	Bronchial LN	Ovaries	F tubes	Uterus	Pituitary	Bladder	Skin	Mammary Gl	Eyes	Spinal cord	Sternum	Nares	Sciatic nerve		
				уу			assessment.																																		
Death	χъ	TK		Histopathology			table for asses																																		
Time on Study	Pι	14			NAD.		No tissue suitable for																																		
90 mg HMX/kg/day				Sample			Eye											_									•	•													
	Animal No: 188 Sex: 9			Clinical History	Right eve dry and half closed from	Weeks 3-5, 7-13.		Right eye partially opaque from	Weeks 6-8.										Necropsy Findings		Right eye sunken in orbit.																				

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Number of Sections Examined		Kidneys Porizonal fat	Lungs	Heart Spleen	Thymus	Salivary Gl	CM Lymph N	Trachea	Thyroids	Parathyroids	Stomach	Duodenum	Ileum	Jejunum	Colon	Rectum	Mesenteric LN	Aorta	Agrenals Bronchial LN	Ovaries	F tubes	Uterus	n adder	Skin	Mammary Gl	Eyes	Spinal cord	Sternum	Nares	Sciatic nerve	
	y																														
Death TK	Histopathology																														
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Project No: 416877 Group: 4 90 mg HMX/kg/day Animal No: 189 Sex: 9	Clinical History	NAD.										Necropsy Findings		CAN																	

Animal No:		•		1000001		•		
	190	0	y hay lang				Number of	
	06.	vex:		14	ТX		Sections Examined	P
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	Clinical	Clinical History	Sample		Histopathology			$\perp$
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NAD.				NAD.			Kidneys Perirenal fat	٦-
							Lungs	7
							Heart	ı
							Spleen	_
							Thymus	1
							Muscle	1
							SALIVARY GI	1-
							Pancreas	
							Trachea	ב
							Thyroids	?
							Parathyroids	1
							Oesophagus	1
				-		-	Stomach	1:
	Necropsy	Necropsy Findings					Duodenum	Ŀ
							Totinim	1
NAD.							milione)	١
							Colon	Ľ
							Rectum	
							Mesenteric LN	크
							Aorta	1
							Adrenals	<u>J.</u>
			•				Bronchial LN	<u> </u>
							Ovaries	7,
							r tubes	1-
							Pituitary	15
							Bladder	
							Skin	
							Mammary Gl	q
							Eyes	4
							Spinal cord	1
							Sterning	<u>~I·</u>
							Nares	-1-
							Sciatic nerve	<u>^r</u>
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	Number of	Sections Examined			Lilvor	Ferfrenal fat	Lunds	Heart	Option	Thymus	Saltvary Gl	SM Lymph N	Pancreas	Trachea	Thyroids	Parathyroids	Orsophagus	Drodenna	11eum	Jejunum	Caecum	Colon	Rectum	Mesenteric LN	Aorta	Adrenals Broochtal I.N	Ovaries	F tubes	Uterus	Pituitary	Bladder	Skin	Mannary GI	Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
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416877 Group:	191			Clinical History														Necrobsy Findings																					
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Death		ТК		Histopathology																																		
Time on Study		14			62	. Gow																																
X/kg/dav				Sample																						•												
No: 416877 Group: 4 90 mg HMX/kg/day		o: 194 Sex: Q		Clinical History		•												Necropsy Findings			•																	
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Death		ЛK		Histopathology																																			
Time on Study		14				NAD.																																	
X/kg/day				Sample																							•												
416877 Group: 4 90 mg HMX/kg/day	0	195 Sex:		Clinical History															Necropsy Findings																				
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K/kg/dav	7 mm /6 m /s			Sample																											•	-													
Project No: 416877 Group: 4 90 mg HMX/kg/day		Animal No: 196 Sex: 9		Clinical History			. CAS														Necropsy Findings		,	NAD.																					

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Death		TK		Histopathology																																				
Time on Study		14				NAD.																																		
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416877 Group:		197 Sex:		Clinical History															Necropsy Findings																					
Project No:	337634	Animal No:			:	NAD.															NAD												_							

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	Number of	Sections Examined			Liver	Perfrenal fat	Lungs	Heart	Thymns	Muscle	ۍ .	SM Lymph N	Trachea	Thyroids	Parathyroids	Oesophagus	Prodenim	Ileum	Jejunum	Caecum	Colon	Merchania IN	Aorta	Adrenals	Bronchial LN	Ovaries	F tubes	Pituitary	Bladder	Skin	Mammary Gl	Eyes Brain	Spinal cord	Sternum	Nares	Sciatic nerve	
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Death	È	TK		Histopathology																																	
Time on Study	,	14			4	NAD.																															
X/kg/day				Sample																					•												
Project No: 416877 Group: 4 90 mg HMX/kg/day	198			Clinical History		NAD.											New Paris	shirpiit i Kedorou		NAU.																	

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Death	ŢĶ		Histopathology																																				
Time on Study	14				NAD.																																		
X/kg/day			Sample																								•												
416877 Group:	199 Sex: Q		Clinical History													i		Necropsy Findings																					
Project No:	Animal No:				NAD.															NAD.																			

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Death		TK		Histopa																																							
Time on Study		14				NAD.																																					
90 mg HMX/kg/day				Sample			,											•											•														
	200			Clinical History		NAD.														Necropsy Findings	Can	. CAN																					

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	Number of Sections Examined			Kidneys Spleen Brain
Death	FD		Histopathology	
Time on Study	r i			NAD.
<b>L</b>	<b>!</b>	ل	Sample	
Project No: 416877 Group: 5 250 mg HMX/kg/day	Sex: Q		Clinical History	NAD.

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	Number of Sections Examined		Liver Spleen Brain
	<del></del> -	76	
Death	TK	Histopathology	
Time on Study	14		JAD.
250 mg HMX/kg/day		Sample	•
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Group:	Sex:	Clinical History	Necropsy Findings
416877	202	Clinical	Necropsy
Project No: 416877	Animal No:		NAD.

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	Number of Sections Examined			Liver Kidneys Spleen	Brain																·	
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Death	ТK		Histopathology																			
Time on Study	14		H18																			
Time		-	_	NAD.								<del></del>		~_				 				-
250 mg HMX/kg/day			Sample						· · · · · ·						•							
Project No: 416877 Group: 5 250 mg H	Animal No: 203 Sex: 9		Clinical History	NAD.							Necropsy Findings	NAD.										
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	Number of Sections Examined		Liver Kidneys Spleen Brain
		Α.	
Death	FD	Histopathology	
Time on Study	12		Not examined.
250 mg HMX/kg/day		Sample	Lungs/Adrenals
Project No: 416877 Group: 5 250 mg H	Animal No: 204 Sex: 9	Clinical History	Necropsy Findings Lungs dark red. Adrenals slightly enlarged and pink.

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	Number of Sections Examined		Liver Kidneys Spleen Brain					
		,						
Death	ТХ	Histopathology						
Time on Study	2.4		NAD.					·
250 mg HMX/kg/day	•	Sample						•
	Sex: 9	Clinical History	NAD.				Necropsy Findings	NAD.

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	Number of Sections Examined			Kidneys Spleen Brain	
ч			Histopathology		
Death	FD		Histopa		
Time on Study	10			NAD.	
250 mg HMX/kg/day			Sample	•	
Project No: 416877 Group: 5 250 mg H	Sex: Q		Clinical History	NAD.	

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	Number of Sections Examined			Liver Kidneys Spleen Brain	 			
Death	FD		Histopathology					
Time on Study	4			NAD.	 ····	 		
250 mg HMX/kg/day			Sample			 		•
: 416877 Group; 5	Animal No: 207 Sex: Q		Clinical History	NAD.			Necropsy Findings	MAD.

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	Number of Sections Examined		-	Kidneys Spleen Brain												i	
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	,		17														,
Death	FD		Histopathology														
Time on Study	6			NAD.													
250 mg HMX/kg/day			Sample									•					
50 mg HA	•	Ī															
'n	<b>~</b>								35								
Group :	Sex:		History						Finding								
416877	208		Clinical History						Necropsy Findings								
Project No:	Animal No:			NAD.						NAD.				· · · · ·	··		

Time, on, Equal Death  14 TK Section Exagined  Histopathology Liver Spleen  Spleen  Brain Spain
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<del>}</del>
Time on Study 14 NAD.
1 1
Sample
Animal No: 209 Sex: 9 Animal No: 209 Sex: 9 Clinical History  NAD.  NAD.

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	Number of Sections Examined		Liver Kidneys Spleen Brain										·
			·										
Death	FD	Histopathology				•							
Time on Study	10		NAD.										
250 mg HMX/kg/day	•	Sample											
Group: 5	Sex: Q	Clinical History					Necropsy Findings						
Project No: 416877	Animal No:		NAD.					NAD.					

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Number of	Sections Examined		Liver Kidneys Spleen Brain								
<b>Death</b> FD		Histopathology						-			
Time on Study D		Hist	Tissues autolytic.								
250 mg HMX/kg/day		Sample					•				
Project No: 416877 Group: 5 250 mg Hi Animal No: 211 Sex: 9		Clinical History	Skull crushed by cage lid.	Necropsy Findings	Skull crushed.	Liver - edge of left lobe pale (10 mm x 5 mm).	Brain - autolysed and too soft to be removed for weighing.				

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	Number of	Sections Examined			Liver	Spleen	Brain															-			_		·		
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Death	4.6	u T		Histopathology		Foci lymphocytes and polymorphs.																							
Time on Study	7	•				Foci lymphocyt																		· · · · · ·		-			
250 mg HMX/kg/dav	• •			Sample		Liver													-		•								
Group: 5	212 Sex: Q			Clinical History												Necropsy Findings													
Project No: 416877	Antmal No:					NAD.							-					NAD.										-	

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	Number of Sections Examined			Liver Kidneys Spleen	Brain						
Death	ТK		Histopathology						·		
Time on Study	14			NAD.		,		··			·
250 mg HMX/kg/day			Sample			-1					•
Group: 5	213 Sex: 9		Clinical History							Necropsy Findings	
Project No: 416877	Animal No:			NAD.				<del>-</del> .			NAD.

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	Number of Sections Examined				·
Death	ТК	Heterocher	Sorous Boosers		
Time on Study	14			NAD.	
250 mg HMX/kg/dav	,	- Lowes	ardinec	•	
Group: 5 250 mg H	<b>~</b>	20000	H. S.Co. J	Findings	
416877	214	Section History		Necropsy Findings	
Project No:	Animal No:			NAD.	

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j	Number of Sections Examined		Liver Kidneys Spleen Brain	
		боду		
Death	KIE	Histopathology		
Time on Study	8		NAD.	
250 mg HMX/kg/day		Sample		•
	Animal No: 215 Sex: Q	Clinical History	Leapt from cage and ran around floor for approximately 15 minutes before collapsing, gasping and convulsing,	NAD.

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	Number of Sections Examined			Liver Kidneys Spleen Brain		-						· · · · · ·	
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Death	FD		Histopathology										
Time on Study	10			NAD.			 						
250 mg HMX/kg/day			Sample						•		-		
	216 Sex: <b>Q</b>		Clinical History				Necropsy Findings						
Project	Animal No:			NAD.				NAD.					

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	Number of	Sections Examined			Liver	Spleen	Brain																					
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Death		FD		Histopathology																								
Time on Study		10				NAD.																						
250 mg HMX/kg/day				Sample																	•							
Project No: 416877 Group: 5 250 mg H	0	Animal No: 217 Sex: V		Clinical History		NAD.									Necropsy Findings		NAD.											

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	Number of Sections Examined		Liver Kidneys Spleen Brain
		y	
Death	FD	Histopathology	
Time on Study	6		NAD.
250 mg HMX/kg/day		Sample	•
Group: 5		Clinical History	Necropsy Findings
Project No: 416877	Animal No:		NAD.

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į	Number of	Sections Examined			Liver Kidneys Spleen Brain
					•
Death		FD		Histopathology	
Time on Study		11			NAD.
250 mg HMX/kg/dav	f== /6			Sample	•
Project No: 416877 Group: 5 250 mg HW	0	 ×		Clinical History	NAD.

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	Number of Sections Examined		Liver Kidneys Spleen Brain
		,	
Death	TK	Histopathology	
Time on Study	14		NAD.
250 mg HMX/kg/day		Sample	•
	Sex: 9	Clinical History	NAD.

Project No: 416877 Group: 6 750 mg HMX/kg/day	X/kg/day	Time on Study	Death			
Animal No: 221 Sex: 9		2	FD		Number of Sections Examined	7
						보
Clinical History	Sample		Histopathology	٨		
NAD.	Liver	Not.examined.			Liver Kidneys Spleen Brain	4-1-m
Necropsy Findings						
Lungs dark red.						<u> </u>
	•					
						<u> </u>

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	Number of Sections Examined		Liver Spleen Brain
Time on Study Death	FD	Histopathology	
X/kg/day		Sample	•
Project No: 416877 Group: 6 750 mg HMX/kg/day	222 Sex: Q	Clinical History	NAD.

	ned	보		M-2-1	$\prod$	
	Number of Sections Examined			Liver Kidneys Spleen Brain		
			λ	·		
Death	FD		Histopathology			
Time on Study	13			Not examined.		
750 mg HMX/kg/day			Sample	Lungs		•
	Sex: 9		Clinical History	NAD.	Necropsy Findings	Lungs dark red with several 1-2 mm white foci on all lobes.

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	Number of Sections Examined			Liver Spleen Spleen Brain
Death	FD		Histopathology	
Time on Study D	3		Hist	NAD.
X/kg/dav			Sample	•
Project No: 416877 Group: 6 750 mg HMX/kg/dav	224 Sex: 9		Clinical History	NAD.

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	Number of Sections Examined			Liver Kidneys Spleen	Brain											
			ology									-				
Death	FD		Histopathology	lytic change												
Time on Study	13			NAD but autolytic change.	Not examined.	····									 	
IX/kg/day			Sample	Liver	Lungs		 					•			 	
Project No: 416877 Group: 6 750 mg HMX/kg/day	Animal No: 225 Sex: 9		Clinical History	NAD.				Necropsy Findings	Liver pale.	Lungs dark red.						

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	Number of Sections Examined			Kidneys	Spleen	brain				<del></del>	 													<del>-, -</del>	
Death	FD		Histopathology																						
			His																						
Time on Study	1			Can																					
K/kg/day			Sample															•							
416877 Group: 6 750 mg HMX/kg/day	226 Sex: 9		Clinical History										Necropsy Findings												
Project No: 416877	Animal No:			NAN	<u>:</u>	_			-					NAD											

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į	Number of Sections Examined			Liver Kidneys Spleen Brain
-			y	
Death	FD		Histopathology	
Time on Study	2			NAD.
X/kg/dav			Sample	•
416877 Group: 6 750 mg HMX/kg/day	o-		Clinical History	Necropsy Findings
Project No: 4				NAD.

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	Number of Sections Examined			Kidneys Spleen			·						÷						
Death	FD	<b></b>	Histopathology																
Time on Study	10		H18																
Time				NAD.		<u> </u>										-	"	<u> </u>	
K/kg/day	·		Sample										•						
Project No: 416877 Group: 6 750 mg HMX			Clinical History	NAD.					Necropsy Findings	NAD.									

	Number of Sections Examined	띺			Kidneys 2 Spleen 1 Brain 3														
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			Histopathology	į															
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(weeks)	2			Not examined.															
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750 mg HMX/kg/day				Lungs				<u></u>	TT	TT		ТТ		T			TT		
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	Sex:		Clinical History						Necropsy Findings	ropsy Findin	ropsy Findin	ropsy Findin	ropsy Findin	ropsy Findin	ropsy Findin	ropsy Findin	ropsy Findin	ropsy Findin	ropsy Findin
	o: 229		Clin						Necr	Necr Lungs dark red.	Necr dark red.	Necr dark red.	Necr dark red.	Necr dark red.	Necr dark red.	Necr dark red.	Necr dark red.	Necr dark red.	Necr dark red.
	Animal No:			NAD.						Lungs	rungs	Lungs							

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Time on Study Death	9 FD		Histopathology	Not examined.		-																		
Time				Not e			 	<del></del>		 			 _				<u>.</u>							-
4X /kα /dav			Sample	Lungs									-		•									
Project No: 416877 Group: 6 750 mg HMX/kg/day	232 Sex: 9		Clinical History	NAD.							Necropsy Findings	finds dark red												

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Death		FD		Histopathology																										
Time on Study		2				NAD.																		_						
IX/kg/dav				Sample	-															•									-	
Project No: 416877 Group: 6 750 mg HMX/kg/day		Animal No: 233 Sex: V		Clinical History		NAD.									Necropsy Findings	NAD.														

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Number of	Sections Examined		1	Liver Kidneys Spleen Brain	
			,		
Death	FD		Histopathology	Focus of non-suppurative cuffing.	
Time on Study	2			Focus of non-s	
4X/kg/day			Sample	Brain	
. 416877	Animal NO: 234 Sex: 8		Clinical History	NAD.	

	1	보		⁷ ~ <del> </del>
	Number of Sections Examined			Liver Kidneys Kjeen Brain
E .			Histopathology	
Death	PD		Histop	
Time on Study	8			NAD.
IX/kg/day			Sample	•
Project No: 416877 Group: 6 750 mg HMX/kg/day	<u>۰</u>		Clinical History	NAD.

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Death	FD			Histopathology																													
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	Sex:			Clinical History													Necropsy Findings																
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Project No:	Animal No:					NAD.												Lungs dark red.															
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	Number of Sections Examined		Liver Kidneys Spleen Brain
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t t		Histopathology	
Death	FD	Histop	
Time on Study	3		NAD.
(/kg/day	•	Sample	•
77 Group:	Sex: Q	Clinical History	Necropsy Findings
Project No: 416	Animal No: 237	10	NAD.

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	·	7	Хb			-																						
Death	FD		Histopathology																									
Time on Study	7			462																								
X/kg/dav			Sample																,	•								
416877 Group;	238 Sex: 9		Clinical History											Necropsy Findings														
Project No:	Animal No:			2			-,			_					CAN					<del></del>								

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	Number of	NECTIONS EXAMINED		Liver Kidneys Spleen Brain		
•	-		y			
Death	FD		Histopathology			
Time on Study	13			Not examined.		
IX/kg/dav	•		Sample	Lungs		•
Project No: 416877 Group: 6 750 mg HMX/kg/day	239 Sex: 9		Clinical History	NAD.	Necropsy Findings	Lungs dark red.

[	ned	보			
	Number of Sections Examined			Spleen Brain	
			hology		
Death	FD		Histopathology		
Time on Study	7			NAD.	
(/kg/day			Sample	•	
750 mg HMX/kg/day					!
Group: 6	r Sex:		History	Necropsy Findings	
416877	240		Clinical History	Necropsy	
Project No: 416877	Animal No:			NAD.	

### APPENDIX 14

HMX: 13 Week Toxicity Study in Mice Methodology of Diet Analysis

### Materials

1,3 Dinitrobenzene (Organic Analytical Standard Grade), BDH Chemicals Limited, Poole.

Acetonitrile (HPLC Grade), Rathburn Chemicals Limited, Walkerburn, Scotland.

### Method

A suitable weight of diet (2.5 g or 5 g) was weighed accurately into a clean glass 8 oz jar. To this was added 1 ml of internal standard solution (dinitrobenzene in acetonitrile at a suitable concentration) and 50 ml of acetonitrile as extracting solvent. The jars were shaken mechanically for 1 h then left to settle, preferably overnight. A suitable aliquot was transferred to a sample vial and analysed by HPLC.

Standard solutions of HMX were prepared by adding a known amount of HMX (equivalent to that of the group being analysed) to a sample of untreated diet. These were treated with internal standard solution and extracting solvent as described for the formulated diet samples.

Three quality control samples were included with each batch of test samples and standards. For this purpose a solution of HMX in acetonitrile was prepared by an independent analyst and these solutions used by the analyst to spike blank samples in exactly the same way as the standards.

### HPLC Conditions

Instrument: Hewlett Packard 1084B with variable wave-

length detector and automatic sampler.

Column: 100 x 5 mm stainless steel packed with ODS

Hypersil (5  $\mu$ ).

Solvent: Acetonitrile: Water (40:60 v/v).

Flow: 1.5 ml/min.

Oven Temperature: 40°C.

Wavelength: 228 nm.

Attenuation:  $2^5 - 2^8$ 

Chart Speed: 0.5 cm/min.

# APPENDIX 15

Methods and Units used in Laboratory Investigations

# **Haematology**

Parameters	Method	Units
Haemoglobin: (Hb)	Drabkin, D.L. and Austin, J.H. J. Biol. Chem., <u>98</u> , 719, (1932).	g/đl
Total Red Blood Cell Count: (RBC)	Coulter Counter, Coulter Electronics Ltd.	x 10 ¹² /1
Packed Cell Volume: (PCV)	Modified Strumia, M.M. et al, Amer. J. Path., 24, 1016, (1954).	8
Absolute Values:		
Mean Cell Volume: (MCV)		fl
Mean Cell Haemoglobin: (MCH)	Haematological Slide Rule	рg
Mean Cell Haemo- globin Concen- tration: (MCHC)		g/dl
Reticulocyte Count:	Visual appraisal using new methylene blue vital staining.	*
Total White Blood Cell Count: (WBC)	Coulter Counter, Coulter Electronics Ltd.	x 10 ⁹ /1
Differential White Cell Count:	Visual appraisal of stained film. (May-Grunwald and Giemsa Stain.)	x 10 ⁹ /1
Heinz Bodies:	Visual appraisal using . methyl violet staining.	

### APPENDIX 15 (continued)

# Clinical Chemistry

Parameters	Method	Units
Urea: (BUN)	Karmen, A., J. Clin. Invest., 34, 131, (1955). Adapted for centrifugal analysis.	mmol/l
Glucose:	Barthelmai, W. and Czok, R., Klin. Wochschr., 40, 585, (1962).	mmol/l
Aspartate Trans- aminase: (GOT) or (AST)	Enzyme Commission of the German Society for Clinical Chemistry. Z. Klin. Chem. Klin. Biochem., 10, 281, (1972). Adapted for centrifugal analysis.	IU/1
Alanine Trans- aminase: (GPT) or (ALT)	Enzyme Commission of the German Society for Clinical Chemistry. Z. Klin. Chem. Klin. Biochem. 10, 281, (1972). Adapted for centrifugal analysis.	IU/1
Lactate Dehydro- genase: (LDH)	Enzyme Commission of the German Society for Clinical Chemistry. Z. Klin. Chem. Klin. Biochem., 10, Jg., 281-291, (1972). Adapted for centrifugal analysis.	1U/1
Sodium: (Na)	I.L. flame photometer	mmol/l
Potassium: (K)	I.L. flame photometer	mmol/l
Total Protein:	Henry, R.J., Sobel, C. and Berkman, S., Anal. Chem., 29, 1491, (1957). Adapted for centrifugal analysis.	g/l
Albumin:	Rodkey, F.L., Clin. Chem., .11, 478, (1965); Dow, D. and Pinto, P.V.C., Clin. Chem., 15, 1006, (1969).	g/l
Alkaline Phosphatase: (AP)	Enzyme Commission of the German Society for Clinical Chemistry. Z. Klin. Chem. Klin. Biochem., 10, 251, (1972). Adapted for	
	centrifugal analysis.	IU/l

### APPENDIX 15 (continued)

### Urinalysis

<u>Parameter</u> <u>Method</u>

pH: Boehringer BM8 Test Strips

Specific Gravity: Refractometer

Protein: Boehringer BM8 Test Strips

Glucose: Boehringer BM8 Test Strips

Ketones: Boehringer BM8 Test Strips

Blood: Boehringer BM8 Test Strips

Bilirubin: Boehringer BM8 Test Strips

Urobilinogen: Boehringer Test Strips

Microscopy: Urine samples centrifuged at 1,000 rpm for

10 min and spun deposit examined for:

epithelial cells (E)

crystals (CR)

white blood cells (W)

erythrocytes (R) organisms (O)

casts (C)

abnormal constituents (A)

For the sake of clarity only the initials E, CR, W, R, O, C and A are used in the

tables of results.

NB Scoring for qualitative urine tests is:

0 = negative

1 = trace amount

2 = small amount

3 = large amount

Colours: PY = pale yellow

GRY = greenish yellow

LY = lemon yellow

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Technician-in-Charge: A. Chalmers

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P. Hudson, F.I.M.L.S.

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Dietary Analysis J.N. Done, B.Sc., Ph.D.

Supervisor:

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